The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper No. 27

Filed by: Merits Panel
Mail Stop Interference
P.O. Box 1450
Alexandria, VA 22313-1450
Tel: 571-272-9797
Fax: 571-273-0042

Filed
13 December 2004

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

JACK S. COHEN, LEN NECKERS, CY STEIN, SHEE L. LOKE, KAZUO SHINOZUKA, GERALD ZON, and MAKOTO MATSUKURA
(U.S. Patent 5,264,423); JACK S. COHEN, LEN NECKERS, CY STEIN, SHEE L. LOKE, and KAZUO SHINOZUKA
(U.S. Patents 5,276,019 and 5,286,717)

(Cohen)[1]

v.

JOHN GOODCHILD and PAUL C. ZAMECNIK
(U.S. Application 08/346,270)

(Goodchild)[2].

Interference 105,040

Before GRON, GARDNER LANE, and NAGUMO, Administrative Patent Judges.

NAGUMO, Administrative Patent Judge.

DECISION - REHEARING - Bd. R. 125

[1] The real party in interest is the United States of America, as represented by the Department of Health and Human Services.

[2] The real party in interest is the University of Massachusetts, Worcester.

Background

October 9, 2002 - Interference 105,040 was declared.

June 29, 2004 - The Board of Patent Appeals and Interferences (hereafter Board) entered its Decisions On Preliminary Motions and Order (Paper No. 104), including an Order Pursuant to 37 CFR § 1.641 that the parties present their views regarding the sua sponte actions by the Board concerning the patentability of Claims 1-20 of Cohen's U.S. Patent 5,286,717 and Claims 9, 10, 20, 21, and 39-42 of Cohen's U.S. Patent 5,264,423 under 35 U.S.C. § 112, first and second paragraphs (Paper No. 104, page 112).

August 9, 2004 - Goodchild filed GOODCHILD ET AL.'S VIEWS WITH RESPECT TO THE BOARD'S SUA SPONTE ACTION (Paper No. 109);

August 9, 2004 - Cohen filed UNITED STATES REQUEST FOR RECONSIDERATION OF DECISIONS ON PRELIMINARY MOTIONS AND ORDER (Paper No. 110).

August 9, 2004 - Cohen filed UNITED STATES RESPONSE TO *SUA SPONTE* REQUEST CONCERNING WRITTEN DESCRIPTION SUPPORT FOR THE UNITED STATES' ONCOGENE CLAIMS (Paper No. 111).

August 18, 2004 - Cohen filed UNITED STATES MOTION 7 (Under 37 C.F.R. § 1.635 Requesting Certificate of Correction)(Paper No. 115).

Discussion

1. The Board's sua sponte actions

Concluding its Decisions On Preliminary Motions and Order (Paper No. 104), the Board entered an Order Pursuant to 37 CFR § 1.641 ordering the parties to present their views regarding sua sponte actions by the Board concerning the patentability of Claims 1-20 of Cohen's U.S. Patent 5,286,717 and Claims 9, 10, 20, 21, and 39-42 of Cohen's U.S. Patent 5,264,423 under 35 U.S.C. § 112, first and second paragraphs, on or before August 9, 2004 (Paper No. 104, page 112). However, the Board did not hold that Claims 1-20 of Cohen's U.S. Patent 5,286,717 and Claims 9, 10, 20, 21, and 39-42 of Cohen's U.S. Patent 5,264,423 are unpatentable under 35 U.S.C. § 112, first and second paragraphs. Rather, the Board invited the parties to comment on the issues raised sua sponte by the Board.

The Board suggested that Claims 1-20 of Cohen's U.S. Patent 5,286,717 and Claims 9, 10, 20, 21, and 39-42 of Cohen's U.S. Patent 5,264,423 "may be unpatentable under 35 U.S.C. § 112, first paragraph, as being based on a specification which fails to provide an adequate written description of the claimed invention" (Paper No. 104, p. 106, second paragraph). The Patent Office must satisfy its initial burden to explain why a patent applicant's claims are unpatentable under 35 U.S.C. § 112,

first paragraph, for noncompliance with its written description requirement. To that end, the Board cited Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), at 563-64, 19 USPQ2d at 1117, for its instruction that a patent applicant's specification "'must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention'" and cited Enzo Biochem, Inc. v. Gen-Prob Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002); Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997); and Fiers v. Revel, 984 F.2d 1164, 1170, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), for their instruction that specifications supporting claims directed to DNA sequences usually provide an adequate written description of the claimed invention under 35 U.S.C. § 112, first paragraph, when they describe the DNA sequences claimed in terms of "structure, formula, chemical name or physical properties" (Paper No. 104, pp. 106-107, bridging para.). In that light, the Board suggested that Cohen's specifications may not adequately describe functional base nucleotide sequences or the claimed inhibitory synthetic sequences complementary thereto without disclosing the structure, formula, chemical name or physical properties of each and every nucleotide of each and every

nucleotide sequence claimed. See, for example, the following statement taken from the Board's Sua Sponte Actions (Paper No. 104, pp. 109-110, bridging para.):

> [W]e point out that the nucleotide sequence of each oncogene differs from another. Thus, the disclosure of a single phosphorothioate-modified antisense oligonucleotide which is said to be complementary with one portion of the c-myc oncogene, and which may or may not be capable of inhibiting the expression or replication of the c-myc oncogene, does not appear to provide an adequate written description of other antisense nucleotide sequences which are complementary with other oncogenes and which are capable of inhibiting the expression or replication of said oncogene. That is, it does not appear that the description of one antisense sequence provides any indication as to the structure (nucleotide sequence) of any other antisense compound encompassed by the genus recited in claims 1-4 and 6-17 (the '717 patent) and claims 9, 20 and 39 (the '423 patent).

The Board's comments stem from its apparent view that persons skilled in the art per se cannot recognize the chemical structures of generically claimed new nucleotide sequences by reference to their function alone. The Board expressly stated (Paper No. 104, pp. 109-110, bridging para.):

> Those skilled in the art cannot recognize, from the description of a single nucleotide sequence, the identity of the other antisense nucleotide sequences which have the claimed function. "Naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." [Regents of the University of California v. Eli Lilly & Co., 119 F.3d at 1566, 43 USPQ2d at 1404.]

In its response, Cohen suggests that the Board has applied a

per se rule for satisfying the written description requirement of 35 U.S.C. § 112, first paragraph, for its claimed invention. Cohen points to testimony in support of its argument that, while the Board's approach may be appropriate for claims drawn to new nucleotide sequences which are complementary to, and inhibit the replication or cytopathic effect of, nucleotide sequences having no recognized order of bases, it is not per se applicable to claimed nucleotide sequences which are complementary to nucleotide sequences having predetermined orders of bases wherein the novelty admittedly resides exclusively in the structural modification of at least one internal phosphate forming the backbone of the nucleotide sequences. Cohen states (Paper No. 111, pp. 3-4; footnote omitted):

> In properly assessing the adequacy of "written description" support for the United States oncogene claims, it is important to understand that the United States does not claim in the involved patents to have invented either oncogenes or antisense per se. At the time of invention, oncogenes were already known to those skilled in the art, as were both unmodified and methylphosphonate modified forms of antisense compounds (Exhibit 2138, Supp. Cowsert Decl., ¶ 11-16, 26, 29; 2140, Supp. Zon Decl., ¶ 12-13, 17).
>
> What the United States inventors did invent was a structural modification (i.e., a phosphorothioate backbone substitution) to antisense compounds which allowed those antisense compounds to more effectively target oncogenes (Exhibit 2138, Supp. Cowsert Decl., ¶ 26; 2140, Supp. Zon Decl., ¶ 12). Since the inventions at issue are not directed to isolation and identification of particular nucleotide sequences, the

> Decision's proposed "all nucleotide sequence" standard is legally incorrect. Under the properly applied law, the United States is only required to provide "written description" support for its invention, i.e., phosphorothioate modifications to improve oncogene targeted antisense, rather than the nucleotide sequence of every antisense compound to which the inventive modification might be applied.

While not denying that its claims are directed to novel compounds, Cohen points to prior art cited in its patent specifications and other information available to persons skilled in the art prior to Cohen's invention which show that: (1) unmodified antisense nucleotide sequences for use in inhibiting the transforming ability, replication and translation of viruses and oncogenes were known in the art at the time Cohen invented the subject matter claimed; (2) methylphosphonate modified antisense nucleotide sequences were recognized in the art generally for use in inhibiting viral protein synthesis at the time Cohen invented the subject matter claimed; and (3) methylphosphonate modified antisense nucleotide sequences had been reported to be effective for selective inhibition of herpes simplex virus type I (HSV-I) at the time of Cohen's invention (Paper No. 111, pp. 5-9). In addition, Cohen submitted a Supplemental Declaration of Dr. Lex M. Cowsert Concerning Written Description (Cohen Exh. 2138, Supp. Cowsert Decl., ¶ 13), Dr. Cowsert being well-recognized in the field of antisense

technology (Cohen Exh. 2134), in support of its argument that, at the time the subject matter claimed in the '717 and '423 patents was invented, persons skilled in the art knew "(1) how to select oligonucleotide sequences which where complementary, or 'antisense', to a desired target, (2) how to synthesize such oligonucleotide sequences and (3) how to test antisense compounds in inhibition assays (Paper No. 111, p. 6, first full para.). Citing Dr. Cowsert's supplemental declaration (Exh. 2138, Supp. Cowsert Decl., ¶¶ 15-16), and Dr. Zon's supplemental declaration (Exh. 2140, Suppl. Zon Decl., ¶ 13), as support, Cohen further argues (Paper No. 111, pp. 6-9):

> [T]he following was known in the art at the time the subject matter of the '717 and '423 patents was invented: (1) the identity of oncogenes, (2) the nucleotide sequences of numerous oncogenes, (3) the existence of homology among various oncogene nucleotide sequences, (4) how to use the known oncogene nucleotide sequences to select antisense targets and (5) how to test the effectiveness of oncogene targeting antisense compounds to oncogene protein expression and in tumor growth inhibition assays.

Moreover, Cohen alleges that each of its patent specifications does provide an adequate written description of complementary phosphothioate modified antisense nucleotide sequences within the scope of the inventions claimed in terms of function, structure, and examples, i.e., not only with words and phrases describing the compounds but also with references to formulae and examples (Paper No. 111, pp. 9-15). Dr. Cowsert's

supplemental declaration supports Cohen's allegation (Cohen Exh. 2138, Supp. Cowsert Decl., ¶ 19).

While mindful of the Board's discussion of instruction provided by the Federal Circuit in Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), and Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), Cohen cites Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) for the axiom that "[c]ompliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed" (Paper No. 111, p. 16, first full para.). Cohen argues that it is not necessary to describe a claimed novel nucleotide sequence in terms of its complete structure, formula, chemical name, or properties. (Paper No. 111, pp. 16-17). Cohen notes Enzo's admonition at 1324, 63 USPQ2d at 1613, "It is not correct . . . that all functional descriptions of genetic material fail to meet the written description requirement." Id. Cohen reminds the Board that it must consider the level of skill in the art, the prior art, and the extent to which the compound's chemical structure, formula, chemical name, physical properties, and functional characteristics, its synthesis and their interrelationships are disclosed in the specification when the

written description requirement of 35 U.S.C. § 112, first paragraph, is at issue. Cohen points to the Federal Circuit's recognition of the same in Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d at 1324, 63 USPQ2d at 1613.

Cohen argues, and cites the supplemental declarations of Cowsert and Zon for the proposition (Paper No. 111, pp. 23-26), that its specifications provide an adequate written description of the claims they support because they disclose "(1) structural formulas illustrating the modified antisense structures being claimed, (2) working examples demonstrating improved efficacy of modified antisense compounds to inhibit the expression of oncogenes and viruses, (3) the invention's applicability to other types of oncogenes and (4) citation to the existing knowledge in the art of both oncogenes and antisense" (Paper No. 111, pp. 23-24, bridging para.). As precedent for its argument, Cohen relies heavily on statements made by the Federal Circuit's decision in Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

In Amgen, 314 F.3d at 1329, 65 USPQ2d at 1397, the Federal Circuit instructed:

> The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined

> to be encompassed within his original creation." . . . [Vas-Cath Inc. v. Mahurkar, 935 F.2d] at 1561, 19 USPQ2d at 1115 . . : . Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.").

At 1330, 65 USPQ2d at 1398, Amgen referred to Enzo Biochem's clarification of Eli Lilly as follows (footnotes omitted):

> [I]n Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge in the art the disclosed function is sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613. Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily misapprehend.

Interestingly, the record before us establishes that neither Cohen's, Goodchild's, nor the Board's deliberations relative to the parties' preliminary motions, especially those asking the Board for conclusions regarding the patentability of claimed nucleotide sequences under 35 U.S.C. § 103 and claims for benefit under 35 U.S.C. § 119 and § 120, have been hindered by any inability to compare the scope of the compounds claimed to prior art compounds. Moreover, neither Cohen, Goodchild nor the Board appears to have been concerned that Goodchild's claims which encompass much, if not all, of the nucleotide sequences of

HTLV-III encompassed by Cohen's claims, are unpatentable for noncompliance with the written description requirement of 35 U.S.C. § 112, first paragraph, even though Goodchild's disclosure may be inferior to Cohen's disclosure for the commonly claimed subject matter. We are concerned that the Board sua sponte focused on the adequacies of the specifications supporting Cohen's claims yet waived consideration of Goodchild's claims on the same ground because of procedural niceties.

Cohen objects that the Board's sua sponte action is unfair, arbitrary and capricious (Paper No. 111, pp 21-23). The objection is not without merit. However, Goodchild, having declined to take any position on the issue raised by the Board (Paper No. 109, p. 1, final para.), will not help us resolve the matter.

When the Board sua sponte rejects a patent applicant's claims under 35 U.S.C. § 112, first paragraph, for noncompliance with its written description requirement, the Board has the initial burden to present evidence and reasons to justify its action. Here, the Board noted that claims in Cohen's '717 and '423 patents are directed to nucleotide sequences and cited and discussed Regents of the University of California v. Eli Lilly & Co., supra, but it did not hold that any of Cohen's claims are unpatentable under 35 U.S.C. § 112, first paragraph, for

noncompliance with its written description requirement. Instead, the Board ordered the parties to present their views on the matter. Cohen briefed the matter (Paper No. 111). Goodchild declined to take a position on the issue (Paper No. 109, p. 1, final para.). Instead, Goodchild proffered other reasons why Claims 1-20 of Cohen's '717 patent are unpatentable for lack of an adequate written description in the supporting specification. Goodchild's filing is therefore irrelevant to the issues raised by the Board.

In any event, the Board had considered matters related to Goodchild's additional critique of Cohen's claims in determining the earliest filing dates to be accorded to subject matter Cohen now claims under 35 U.S.C. § 120 in consideration of Goodchild's preliminary motions under 37 CFR § 1.633(a) for conclusions as to the patentability of subject matter Cohen claims over art. See, for example, pages 10-23 of the Board's Decisions on Preliminary Motions (Paper No. 104, pp. 10-24). If Goodchild did not timely question the patentability of the subject matter Cohen claims under 35 U.S.C. § 112, first paragraph, when comparing the scope and content of Cohen's claims to prior art disclosures, we fail to see why it should be allowed to do so at this time. Goodchild declined to take a position on the issues raised by the Board. Accordingly, we decline to consider, at Goodchild's belated

behest, whether the subject matter Cohen claims is adequately described in Cohen's latest supporting specification for other reasons.

We are grateful for, and considerate of, Cohen's views on the issue raised sua sponte by the Board. We are particularly impressed by the distinctions the Federal Circuit made between the results in the Eli Lilly and Enzo Biochem cases discussed by the Board and the result in Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003) (footnote omitted):

> Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.

The distinction the Federal Circuit recognized between the holdings in Eli Lilly and Amgen Inc. v. Hoechst Marion Roussel Inc., supra, has a long and substantial history. The Court of Customs and Patent Appeals said in In re Metcalfe, 410 F.2d 1378, 1383, 161 USPQ 789, 793 (CCPA 1969)(emphasis added):

> As we also pointed out above, the . . . properties, rather than the chemical identity of a given resin, are here important in determining its suitability for use in appellants' invention. In appropriate cases, such as this, where the chemical identity of the material is not critical, we see no reason why applicant should not be permitted to define that material partly in terms of its physical properties or the function which it performs.

The Court of Customs and Patent Appeals stated in In re Chilowsky, 229 F.2d 457, 460, 108 USPQ 321, 324 (CCPA 1956):

> It is well settled that the disclosure of an application embraces not only what is expressly set forth in words and drawings, but what would be understood by persons skilled in the art. As was said in Webster Loom Co. v. Higgins et al., 105 U.S. 580, 586 [(1881)], the applicant "may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out in the patent and delineated in the drawings."

Cohen's and Goodchild's responses to the Board's Order Pursuant to 37 CFR § 1.641 to the parties to present their views regarding its sua sponte action selectively questioning the patentability of Claims 1-20 of Cohen's U.S. Patent 5,286,717 and Claims 9, 10, 20, 21, and 39-42 of Cohen's U.S. Patent 5,264,423 under 35 U.S.C. § 112, first paragraph (written description requirement), differ significantly. Cohen argues that the partial structures, functional characteristics, and examples of nucleotide sequences in its patent specification provide an adequate written description of Cohen's claims. Cohen argues that its case is inapposite to that presented in Eli Lilly and Enzo Biochem for reasons recognized by the Federal Circuit in Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d at 1330, 65 USPQ2d at 1398. According to Cohen, the Board did not consider the facts peculiar to Cohen's case, did not consider all

applicable precedent, and therefore, did not adequately consider any distinctions between Cohen's case and that presented in Eli Lilly. Cohen also objected that the Board acted unfairly, arbitrarily, and capriciously when the Board sua sponte raised the issue, with respect to Cohen only, of whether Cohen's specifications provide an adequate written description of the nucleotide sequences both parties claim.

We conclude from our review of the record that the Board, apparently aware of the difficulties in the area of the law, did not hold that Cohen's claims were unpatentable. Rather, it ordered the parties to present their views on the new issue. Cohen's traverse of the Board's basis for raising the new issue of unpatentabilty is cogent, fact-oriented, and supported by precedent at least as pertinent to Cohen's case as the precedent the Board relied upon. Cohen's traverse is also unchallenged, as Goodchild declined to discuss the issues raised by the Board. To the extent that the Board set forth a prima facie case for unpatentability based on the reasons raised in our Decisions On Preliminary Motions and Order (Paper No. 104), that case has been seriously questioned, if not undermined. Accordingly, we withdraw the issues raised sua sponte by the Board.

2. Reconsideration of Decision on Cohen's Preliminary Motion 5

The Board denied Cohen's Preliminary Motion 5 under 37 CFR § 1.633(c)(4) (Paper No. 48) to have Claims 9, 10, 20, 21, and 39-42 of involved U.S. Patent 5,264,423 and Claims 1-20 of involved U.S. Patent 5,286,717 "designated as not corresponding to Count 1" (Paper No. 104, pp. 101-105). Cohen requests reconsideration of the Board's decision for a variety of reasons (Paper No. 110, pp. 1-5).

Cohen argues that it acted in accordance with Section 26(j) of the Board's Standing Order (Paper No. 3), entered October 9, 2002, which reads in pertinent part:

> A party's Rule 633(c) preliminary motion seeking to have its claim designated as not corresponding to a count shall establish that the claim covers an invention which is not the same patentable invention as any of the opponent's claim [sic] designated as corresponding to a count.

Thus, Cohen argues that, to the extent its Preliminary Motion 5 (Paper No. 48), and evidence in support thereof, established that its claimed oncogene inventions cover an invention which is not the same patentable invention as any of the opponent's claims designated as corresponding to the Count 1, Cohen's Preliminary Motion 5 should have been granted and the Board erred in denying the same (Paper No. 110, Para. IIB, pp. 3-4). According to Cohen (Paper No. 110, pp. 3-4, bridging para.; emphasis Cohen's):

> The standing Order states that the moving party need only "establish that the claim covers an invention which is not the same patentable invention as any of the opponent's claim designated as corresponding to a count" . . . . As the decision acknowledges, the United States has met the requirements of the Standing Order for its Motion 5. There is nothing in the Standing Order which then requires that the United States further show that its claimed oncogene inventions are not the same patentable invention as the United States' own claims corresponding to the count.

The resolution of this issue requires us to determine which regulations govern our deliberations. This interference was declared on October 9, 2002, under 37 CFR (2002). In the intervening time, two signal events occurred regarding the law of corresponding claims. First, the Federal Circuit interpreted the rules then in effect as requiring that correspondence be determined under a "two-way" (or mutual unpatentability) test between the claims sought to be removed and those that are not:

> In determining whether it is proper to designate an application or patent claim to correspond to a count, the pertinent inquiry is whether that "claim defines the same patentable invention as another claim whose designation as corresponding to the count the moving party does not dispute." [37 C.F.R.] §1.637(c)(3)(ii). In that regard, what constitutes the "same patentable invention" is defined by 37 C.F.R. § 1.601(n), which was formulated to determine the extent of interfering subject matter as between applications (or a patent application and an issued patent) of potentially conflicting parties. See In re Van Geuns, 988 F.2d 1181, 1185 (Fed. Cir.1993). Accordingly, the two-way test promulgated pursuant to 37 C.F.R. § 1.601(n), as discussed above, Part III.B, supra, is applied to determine whether a claim is properly designated to correspond to the count.

Eli Lilly v. Board of Regents of the Univ. Wash., 334 F.3d 1264, 1271, 67 USPQ2d 1161, 1166 (Fed. Cir. 2003) (cert. denied, ___ U.S. ____, 124 S. Ct. 1713 (2004)). That is, a claim corresponds to the count if it is unpatentable over a claim that undisputedly corresponds to the count, and vice-versa. The Standing Order sets forth the Board's interpretation of the regulations and controls proceedings before the Board in this interference to the extent that it is not inconsistent with the regulations or the statute. Section 26(j), which focuses on the existence of claims that interfere with claims in the opponent's application or patent, is not inconsistent with the regulations as interpreted by the Federal Circuit. Under the standard of Rule 26(j), as governed by the Federal Circuit's decision in Eli Lilly, Cohen's burden was to show that the claims of the '717 patent were neither anticipated nor obvious over Goodchild's claims, and that Goodchild's claims were neither anticipated nor obvious over the claims of Cohen's '717 patent.

The second signal event was the promulgation of new regulations covering practice before the Board of Patent Appeals and Interferences.[3] 69 FED. REG. 49,960, 50,020 (August 14, 2004,

[3] The Federal Circuit has expressly recognized the authority of the Director to promulgate rules governing the practice before the office in interferences. Medichem, S.A. v. Rolabo, S.L., 353 F.3d 928, 69 USPQ2d 1283 (Fed. Cir. 2003) ("We are aware that the PTO has issued a notice of proposed rulemaking, with proposed § 41.203(a) clarifying the interference-in-fact

effective September 13, 2004: "2004 Rules"). The 2004 rules define interfering subject matter via a mutual unpatentability test. 37 CFR § 41.203(a)[4]; 69 FED. REG. at 50,019; accord, Eli Lilly, 334 F.3d at 1270, 67 USPQ2d at 1165 (approving the Director's mutual unpatentability standard.) The new definition of corresponding claims, however, is based on the scope of estoppel that attaches to an adverse judgment as to priority for the count. See 37 CFR § 41.207(b)(2) (2004).[5] Thus, under the 2004 rules, corresponding claims are those claims that are unpatentable with respect to the (potentially lost) count. The count, of course, may be defined by claims taken from any involved application or patent.

Following the guidance of the Federal Circuit, we apply the rules in effect at the time of our decision except when the affected parties have relied on the former rules. Singh v. Brake, 222 F.3d 1362, 1371, 55 USPQ2d 1673, 1679 (Fed. Cir. 2000)

---

standard. See Rules of Practice Before the Board of Patent Appeals and Interferences, 68 Fed. Reg. 66,664, 66,664-65. Our opinion in this case should not be read to require any particular result or otherwise influence in any way the outcome of the PTO's rulemaking.").

[4] 37 CFR § 41.203(a) Interfering subject matter. An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa.

[5] 37 CFR § 41.207(b)(2) A claim corresponds to a count if the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim.

("Because no reliance interests by either party are impacted by the PTO's new procedural rule with respect to the Board's review of an APJ's interlocutory orders, we instruct the Board to apply the new standard, embodied in the current version of 37 C.F.R. § 1.655(a), on remand.") (citations omitted, emphasis added).

In the present case, Cohen's reliance interest is clear, as the change in the rule might well be outcome-determinative due to the different standard for determining claim correspondence. Accordingly, we are constrained to apply the 2002 regulations as construed by the Federal Circuit.

Cohen, as the moving party, bears the burden of proof by a preponderance of the evidence. We agree with Cohen that the Board found that Goodchild's HIV specific claims do not anticipate Cohen's oncogene specific claims. (Paper No. 104 at 103.) We do not agree, however, that the Board "effectively found that the United States oncogene specific claims were patentably distinct from opponent Goodchild's involved HIV specific claims." (Paper No. 110 at 3.) Rather, the Board determined that, having failed to carry what it perceived Cohen's burden to be, even if Cohen's argument with respect to Goodchild's HIV specific claims was correct, it would not be a sufficient basis on which to grant Cohen's motion. (Paper

No. 104 at 105.) Here, Cohen appears to be correct when it urges that the Board deviated from the Standing Order, § 26.

Accordingly, we consider the merits of Cohen Preliminary Motion 5. There appear to be two major issues at the core of the question of (mutual) obviousness of the oncogene-specific claims over the HIV-specific claims. The first issue is the definition of the term "oncogene." Cohen provides the definition, "[o]ncogenes are genes whose products have the ability to transform eukaryotic cells so that they grow in a manner analogous to tumor cells." (Cohen Exh. 2024 at 3, ¶ 7, citing Lewin, Genes V, at 1249 (Cohen Exh. 2027); Goodchild's definition does not differ significantly – see Cohen Exh. 1027, ¶ 32 ("the term 'oncogene' is defined as a mutated and/or overexpressed version of a normal gene of animal cells that can cause cancer.").) Cohen preliminary motion 5 urges that "[s]ometimes oncogenes may be carried by a retrovirus, but oncogenes are not known to be carried by the HIV genome." (Paper No. 48 at 14, citing testimony by its expert, Dr. Lex M. Cowsert, Cohen Exh. 2024, ¶ 8 ("Cowsert").) Thus, Cohen denies that the subject matter claimed by Goodchild anticipates any of its claims covering oncogene modified-antisense polynucleotides.

Goodchild, in opposition, argues that it has demonstrated that the "tat" gene and the "c-myc" gene are "substantially the

same to each other and to oncogenes in the context of antisense technology." (Paper No. 62 at 20.) Goodchild's arguments are supported by the testimony of Dr. Kandimalla (Goodchild Exh. 1024, "Kandimalla") and the Kim abstract (Goodchild Exh. 1025) and the CancerGene Homepage (Goodchild Exh. 1026), both cited by Kandimalla. Cohen, in reply, urges that the complete Kim article belies the conclusion that the tat gene is necessarily "transforming," and therefore an oncogene. (Cohen Reply 5, Paper 90 at 4-5, citing Cowsert declaration, Cohen Exh. 2100, ¶ 10.) Moreover, Cowsert cites current scientific databases and recent articles as being inconsistent with the status of tat as an oncogene. (Cohen Exh. 2100, ¶¶ 5-9.)

While Cohen criticizes Goodchild for providing only the abstract of the Kim article, Cohen's quotation is selective and less than persuasive. The complete first paragraph of the discussion section reads:

> This study provides direct evidence for the ability of the HIV tat gene to transform human keratinocytes in culture. It is not clear from this study whether the immortalized state of the RHEK-1 cells or the function of the SV40 T antigen encoded by the Ad 12-SV40 hybrid virus plays a role in the transformation process. However, there has been no previous evidence for either the HIV Tat protein transactivating the adenovirus promoters or the SV40 T antigen turning on the HIV LTR. We are presently attempting to transform primary human keratinocytes with the HIV tat gene in the absence or presence of other known oncogenes. [Cohen Exh. 2105 at 1526.]

The nature of the "transformation" is clarified by the first sentence of the immediately preceding paragraph: "While control RHEK-1 cells and tat-negative clones have a flat morphology when grown as monolayers in culture, . . . the tat-positive clones as a group have a tendency to pile up and form balls of cells of varying sizes under similar growth conditions." (Id.) On the limited record before us, we are not inclined to agree with Cohen's insinuation that the abstract is a misrepresentation of the substance of the article. But we do find that "direct evidence for the ability of the HIV tat gene to transform human keratinocytes in culture" is not the same as a finding that the product of the tat gene is an oncogene, i.e., that it causes cancer. Consistently, Cowsert testified that "[c]urrent scientific literature does not presently recognize HIV-1 tat as an oncogene" (Cohen Exh. 2100 at ¶6), citing a review article published in 2002 (Cohen Exh. 2101).

Weighing the testimony of Kandimalla and the Kim abstract (the CancerGene reference appears to be cumulative with Kim) against the testimony of Cowsert and the complete Kim article, as well as the other literature cited by Cowsert, we find the preponderance of the evidence indicates that the HIV tat-gene is not generally regarded as an oncogene. In particular, we find that being recognized as a "factor in the progression" of AIDS-

related Kaposi's sarcoma is not sufficient to elevate HIV-tat to the status of being an oncogene. If the status of the HIV tat gene was not unequivocally an oncogene in 2002, it is not plausible, in the absence of direct statements, that it was regarded as an oncogene in the late 1980s. Accordingly, we find no reason to disturb the Board's conclusion that HIV genes are not oncogenes, and that antisense compounds to one do not anticipate antisense compounds to the other.

The second issue is whether the modified antisense polynucleotides to oncogenes claimed by Cohen would have been obvious over the modified antisense polynucleotides to HIV claimed by Goodchild. Cohen focuses its attention on the question of whether there would have been

> a reasonable expectation of success[fully making] phosphorothioate antisense oligonucleotides useful for inhibiting oncogene nucleic acids (as in claims 1-20 of the United States '717 patent and claims 9, 10, 20, 21, and 39-42 of the United States '423 patent) in view of oligonucleotide compounds complementary to the RNA or DNA of HIV, as defined by the claims of Goodchild's involved claims 17-19, 21-25, 27, 44-46, 48-52, 54-56, 58, 61 and 64. [Paper No. 48 at 15.]

In support of the alleged unpredictability of the art, Cohen argues, citing testimony by Cowsert, that "[a] cell susceptible to or undergoing transformation due to an oncogene would not have the same biological changes, including changes to membrane permeability to phosphorothioate antisense oligonucleotides that

would occur in virally-infected cells." (Paper No. 48 at 16.) Essentially the identical sentence is found in Cowsert's testimony (Cohen Exh. 2024 at ¶ 9.) Cowsert, however, does not explain the experimentally verified basis for this statement, nor does he provide citations to the literature indicating that this statement is generally accepted. Accordingly, we are unable to give this argument significant weight. Cohen bears a positive burden to establish the factual basis underlying its position that the two sets of claims are mutually nonobvious. Because Cohen failed to establish the factual underpinnings supporting its motion, Cohen preliminary motion 5 is DENIED.

3. Has 35 U.S.C. § 112 been equally applied to both parties?

Cohen complains that the Board unfairly, arbitrarily and capriciously applied a higher standard to Cohen in finding that its involved patent specifications and the specifications of the parent applications of its patents might not satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, for the inventions defined by Cohen's involved claims, than it applied to Goodchild in finding that Goodchild's involved application and the specifications of Goodchild's parent U.S. and PCT applications satisfied the written description requirement of 35 U.S.C. § 112, first paragraph, for the inventions defined by Goodchild's's involved claims. The suggestion that Cohen's

complaints have merit is supported by the Board's sua sponte action against Cohen's involved claims while excusing Goodchild's claims directed to the same patentable invention from similar action seemingly because of Cohen's procedural shortcomings. At Cohen's urging, we have reviewed the entire record. Based on our review, we find certain inconsistencies and errors in the Board's original findings of fact and conclusions of law which demand reconsideration of the merits of Goodchild's preliminary motions under 37 CFR § 1.633(a).

Accordingly, our review leads us to analyze the adequacy of the written descriptions and enablement provided in the various specifications for the involved claims of both parties. We then proceed to determine whether Cohen's U.S. Patent 5,276,019 is prior art to the subject matter defined by any of Goodchild's claims corresponding to Count 1 and whether Goodchild's U.S. Patent 4,806,463 is prior art under 35 U.S.C. § 102(b) to all of Cohen's claims designated as corresponding to Count 1 and thus bars consideration of Cohen's attempts under 37 CFR § 1.131 to antedate Goodchild's patent as a prior art reference. Next, we shall consider whether Goodchild's involved claims are patentable over prior art of record. Finally, we shall determine whether the subject matter Cohen claims is unpatentable under 35 U.S.C. § 103 in view of the combined prior art of record, including

Goodchild's patent. Our goal is to determine precisely what commonly claimed subject matter is patentable to both parties and to establish a count in this interference for properly determining priority of invention for interfering subject matter patentable to both parties to this interference proceeding.

4. Are Cohen's patents prior art to any of Goodchild's claims?

According to Cohen, its involved U.S. 5,264,423, patented November 23, 1993, which issued from Application 07/976,733, filed November 16, 1992, is a continuation of Application 07/159,017, filed February 22, 1988, which is a continuation-in-part of Application 07/030,073, filed March 25, 1987. According to Cohen, involved U.S. 5,286,717, patented February 15, 1994, which issued from Application 07/976,777, filed November 16, 1992, is a division of Application 07/159,017, filed February 22, 1988, which is a continuation-in-part of Application 07/030,073, filed March 25, 1987. According to Cohen, its involved U.S. 5,276,019, patented January 4, 1994, which issued from Application 07/159,017, filed February 22, 1988, is a continuation-in-part of Application 07/030,073, filed March 25, 1987.

Because the specification of Cohen's U.S. 5,276,019, patented January 4, 1994, which issued from Application 07/159,017, filed February 22, 1988, is common to both U.S.

5,264,423 and U.S. 5,286,717, we need only consider whether U.S. 5,276,019 is, on its face, prior art to subject matter claimed in Goodchild's U.S. Application 08/346,270, filed November 23, 1994. Since Cohen's Application 07/159,017 was filed February 22, 1988, and Cohen's '019 patent issued therefrom on January 4, 1994, Cohen's '019 patent is prior art to the subject matter Goodchild claims in its involved Application 08/346,270 under 35 U.S.C. §§ 102(a) and (e) unless Goodchild both claims and perfects its claims for benefit of the filing dates of its previously filed applications under 35 U.S.C. §§ 119, 120, and 121.

According to Goodchild, its involved U.S. Application 08/346,270, filed November 23, 1994, is a continuation of Application 07/882,073, filed May 12, 1992, which is a continuation of Application 07/798,263, filed November 18, 1991, which is a continuation of Application 07/160,574, filed February 26, 1988. Given the February 22, 1988, filing date of Cohen's 07/159,017 application, Cohen's U.S. 5,276,019 remains prior art to Goodchild's involved claims under 35 U.S.C. § 102(e) unless Goodchild perfects its claims[6] for benefit under 35 U.S.C.

---

[6] A patent applicant's claim for benefit of the filing date or an earlier filed application under 35 U.S.C. § 120 or § 119 for later claimed subject matter is perfected by establishing that the specification of the earlier filed

§ 120 of the earlier filing date of Application 07/071,894, filed July 10, 1987 (from which, according to Goodchild, Application 07/160,574 continues-in-part), benefit under 35 U.S.C. § 119 of the earlier filing date of PCT/US87/01211, filed May 22, 1987 (now WO87/07300 (Goodchild Exh. 1010), published December 3, 1987)(see Goodchild's Preliminary Motion 8 (Paper No. 40) and the Board's decision granting that motion (Paper No. 104, pp. 77-81)), and/or benefit under 35 U.S.C. § 120 of the filing date of Application 06/867,231, filed May 23, 1986 (from which, according to Goodchild, Application 07/071,894 continues-in-part).

---

application satisfies the requirements of 35 U.S.C. § 112 for the full scope of the subject matter claimed. See In re Gosteli, 872 F.2d 1008, 1010, 10 USPQ2d 1614, 1616 (Fed. Cir. 1989):

> The reference to the "invention" in section 119 clearly refers to what the claims define, not what is disclosed in the foreign application. Cf. In re Scheiber, 587 F.2d 59, 61, 199 USPQ 782, 784 (CCPA 1978)(stating that "invention" as used in 35 U.S.C. § 120 . . . refers to what is claimed). Section 119 provides that a foreign application "shall have the same effect" as if it had been filed in the United States. 35 U.S.C. § 119. Accordingly, if the effective filing date of what is claimed in a United States application is at issue, to preserve symmetry of treatment between sections 120 and 119, the foreign priority application must be examined to ascertain if it supports, within the meaning of section 112, ¶ 1, what is claimed in the United States application.

Claims 17[7] and 61 of Goodchild's involved application are directed respectively to oligonucleotides and compositions for inhibiting replication or gene expression of HTLV-III in a cell. In particular, independent Claim 17, from which all other claims depend, includes the requirement (b) that the phosphate modification does "not prevent . . . uptake into infected cells." The oligonucleotide consists of a nucleotide sequence of 14 to 50 nucleotides complementary to a region of RNA or DNA of HTLV-III necessary for its replication, gene expression, or both. A critical element of the claimed oligonucleotide is that one to all of its internal phosphate groups are modified in such a way that the intended purpose and utility of the complementary nucleotide sequence is retained. Claims 18, 19, 21-25 and 27 further functionally or structurally limit the oligonucleotides

---

[7] 17. An oligonucleotide consisting of a nucleotide sequence of 14 to 50 nucleotides complementary to a region of RNA or DNA of HTLV-III, wherein the region of RNA or DNA is selected from the group consisting of regions necessary for replication of HTLV-III, regions necessary for gene expression of HTLV-III, and regions necessary for both replication of HTLV-III and gene expression of HTLV-III, wherein one to all internal phosphate groups of said oligonucleotide are modified such that the modified phosphate groups do not prevent (a) inhibition of HTLV-III replication, gene expression or both, (b) uptake into infected cells, (c) inhibition of degradation of the oligonucleotide, (d) prevention of the use of the oligonucleotide as a primer by reverse transcriptase, or (e) any combination thereof.

of Claim 17 as to nucleotide sequence length, number of modifications, and/or particular function without specifying the structural nature of the phosphate modification. Significant to the present inquiry are Claims 44-46, 48-52, 54-56, 58 and 64, which further limit the modified internal phosphates of the oligonucleotides of Claims 17-19, 21-25 and 27 upon which they depend, to phosphorothioates (Paper No. 10). For example, see dependent Claim 44.[8] Goodchild's U.S. 4,806,463, which was filed May 23, 1986, generically describes oligonucleotides consisting of a nucleotide sequence of 14 to 50 nucleotides complementary to a region of RNA or DNA of HTLV-III necessary for its replication, gene expression, or both, and compositions thereof for inhibiting replication or gene expression of HTLV-III in a cell (Goodchild's '463 patent, col. 1, l. 56-64; col. 5, l. 14-28). Goodchild's '463 patent further teaches the oligonucleotides may be modified at one to all of their internal phosphate groups in such a way that the intended purpose and utility of the complementary nucleotide sequence is retained (Goodchild's '463 patent, col. 5, l. 29, to col. 6, l. 12). We find, however, no explicit or implied disclosure therein that the modified internal phosphate

[8] 44. An oligonucleotide according to claim 17, wherein the modified internal phosphate group or groups is a phosphorothioate.

group or groups of the complementary nucleotide sequences may be a phosphorothioate group or groups.

We must find a description of a nucleotide sequence complementary to RNA or DNA of HTLV-III, wherein one or more of the internal phosphate groups is replaced by a phosphorothioate group or groups, either in Goodchild's Application 07/071,894, filed July 10, 1987, or PCT/US87/01211, filed May 22, 1987 (now WO87/07300 (Goodchild Exh. 1010), published December 3, 1987), in order for Goodchild to antedate Cohen's U.S. Patent 5,276,019, filed February 22, 1988, as prior art under 35 U.S.C. § 102(e) with respect to the invention of Claims 44-46, 48-52, 54-56, 58 and 64 of Goodchild's Application 08/346,270 designated as corresponding to Count 1. We have searched Goodchild's Application 07/071,894, filed July 10, 1987 (Cohen Exh. 2016) for pertinent disclosure. We found the following sentence at page 13, lines 23-27 (Cohen Exh. 2016, p. 13, l. 23-27):

> It would be particularly desirable to permanently modify the target site by attaching to the hybridon chemically reactive groups capable of crosslinking, cleaving or otherwise modifying the target site.

On pages 14 and 15 of Goodchild's Application 07/071,894, we found the following two paragraphs (Cohen Exh. 2016, p. 14, l. 20, to p. 15, l. 7):

> It has now been demonstrated that 3' or 5' exonucleases, such as phosphodiesterases from snake venom

> or spleen, can progress past a single methylphosphonate internucleoside linkage. It has also been shown that two such linkages in succession constitute a strong block to the enzyme's activity and can increase the half life of an oligomer in the presence of such an enzyme by 100 fold. Good protection from destruction of oligodeoxynucleotide by exonucleases can be afforded by using methylphosphate linkages at the last two positions at each end of the molecule. This enhances the survival of the compound in vivo.
>
> Another modification known to inhibit nuclease digestion is the replacement of internucleoside phosphate by thiophosphate. Matzura, H. And F. Eckstein, European Journal of Biochemistry, 3:448 (1968). Thus, some or all of the phosphates in an oligonucleotide sequence can be replaced by thiophosphate to suppress nucleolytic degradation.

No claims in Goodchild's Application 07/071,894 are explicitly directed to oligonucleotides consisting of nucleotide sequences complementary to a region of RNA or DNA of HTLV-III, wherein the modified internal phosphate group or groups of the complementary nucleotide sequences may be a phosphorothioate group or groups.

Next, we searched Goodchild's PCT/US87/01211, filed May 22, 1987 (now WO87/07300 (Goodchild Exh. 1010), published December 3, 1987). There, we found the same sentence (Goodchild Exh. 1010, p. 13, l. 15-19) and same two paragraphs (Goodchild Exh. 1010, p. 14, l. 13-32) found in Goodchild's Application 07/071,894.

Related to our inquiry, we note that a substantial portion of the invention described in Goodchild's Application 07/071,894 and PCT/US87/01211 is disclosed in Zamecnik et al. (Zamecnik '86

article), "Inhibition of replication and expression of human T-cell lymphotropic virus type III in cultured cells by exogenous synthetic oligonucleotides complementary to viral RNA," Proceedings of the National Academy of Sciences, Vol. 83, No. 12, pp. 4143-4146 (June 1986), said to be contributed by Paul C. Zamecnik on February 7, 1986 (Cohen Exh. 2030, p. 4143), and Paul C. Zamecnik's NIH grant application (Zamecnik's NIH Grant Application) entitled "Oligonucleotide Inhibition of HTLV-III" Virus in Culture, signed March 10, 1986, stamped received March 11, 1986 (Cohen Exh. 2039, p. 1), and made available to the public on September 30, 1986. See the Board's findings (Paper No. 104, p. 62). Zamecnik's '86 article, published in June 1986 reports, "Miller, Ts'o, and collaborators . . . have been using synthetic oligodeoxynucleotides, modified as the methyl-phosphonates, to inhibit herpes virus replication" (Cohen Exh. 2030, p. 4143, col. 2). According to Zamecnik, the paper "show[s] that complementary synthetic oligodeoxynucleotides directed toward different regions of the HTLV-III genome inhibit virus replication and gene expression in culture HTLV-III-transformed human lymphocytes" (Cohen Exh. 2030, p. 4143, col. 2).

We find in Zamecnik's '86 article no explicit teaching or reasonable suggestion of oligonucleotides consisting of

nucleotide sequences complementary to a region of RNA or DNA of HTLV-III, wherein the modified internal phosphate group or groups of the complementary nucleotide sequences may be a phosphorothioate group or groups. However, Zamecnik's NIH Grant Application states, as justification for a research associate (Cohen Exh. 2039, p. 9):

> Our synthetic plans for oligonucleotides consist of two parts: (1) synthesis and purification of large amounts of selected unmodified oligonucleotide sequences. (2) The synthesis of phosphonate and thiophosphonate modifications of oligomers, and when successful, their scale-up.

According to the plan outlined in Zamecnik's NIH Grant Application (Cohen Exh. 2039):

> (3) Internucleotide Phosphate and Other Modifications: This may be the most desirable function to block as the resulting, non-charged oligonucleotides are taken up by the cells more readily, are more resistant to enzymatic degradation, and retain the ability to form Watson-Crick base pairs, although the chirality of modified internucleotide phosphates results in a mixture of atactic oligonucleotides having a spread in their affinities for target RNA. Dr. Letsinger will discuss newer, innovative triester internucleotide modifications (21) in his companion application.
>
> In our laboratory, we intend to use the procedure of Miller et al. to synthesize oligonucleotide methyl phosphonates (22). A third phosphate modification, the replacement of P=O by P=S, does not alter the charge on the molecule but may increase resistance to degradation (23). This modification can be introduced during automatic synthesis (24).
>
> As phosphate modification can result in solubility problems, it will be necessary to investigate the ratio of modified to unmodified phosphates to optimize activity.

Based on all the evidence of record, we find that neither Goodchild's Application 07/071,894, filed July 10, 1987 (U.S. Exh.2016), nor PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010), describes, or reasonably would have enabled persons skilled in the art to make and use, the full scope of the invention of Claims 44-46, 48-52, 54-56, 58 and 64 of Goodchild's Application 08/346,270, which stand designated as corresponding to Count 1 of this interference. As we held supra, every Goodchild claim encompasses a limitation that the modified phosphate - oligonucleotide(s) do not inhibit uptake by a cell or are active within a cell. First, the evidence does not establish that Goodchild had possession of the phosphorothiolates of the invention now claimed at the time it filed either Goodchild's Application 07/071,894, filed July 10, 1987 (Cohen Exh. 2016), or PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010). While Goodchild's earlier applications disclose that "some or all of the phosphates in an oligonucleotide sequence can be replaced by thiophosphate to suppress nucleolytic degradation" (Cohen Exh. 2016, p. 15, 5-7; Goodchild Exh. 1010, p. 14, l. 30-32), it appears from the evidence as a whole that, based the disclosures of Goodchild's Application 07/071,894, filed July 10, 1987 (Cohen Exh.2016), and PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010), persons skilled in the art reasonably would

not have understood that Goodchild had possession of the phosphorothiolates of the invention Goodchild now claims. Moreover, such persons reasonably could not have predicted success for the full scope of phosphorothiolates of the invention Goodchild now claims without undue experimentation. Goodchild presently claims that oligonucleotides consisting of a nucleotide sequence of 14 to 50 nucleotides complementary to a region of RNA or DNA necessary for HTLV-III replication or gene expression, wherein one or all internal phosphate groups are replaced by thiophosphate groups, "do not prevent (a) inhibition of HTLV-III replication, gene expression, or both, (b) uptake into infected cells, (c) inhibition of degradation of the oligonucleotide, (d) prevention of the use of the oligonucleotide as a primer by reverse transcriptase, or (e) any combination thereof" (Claim 17 of Goodchild's Application 08/346,270; emphasis added).

Zamecnik's NIH Grant Application itself supports the view that undue experimentation would have been required to make and use charged thiophosphate-modified nucleotide sequences in the same manner or to the same extent as the corresponding uncharged methylphosphate nucleotide sequences complementary to a region of RNA or DNA of HTLV-III described by "Miller, Ts'o, and collaborators" (Zamecnik's '86 article, p. 4143, col. 2; Zamecnik's Grant Application (Cohen Exh. 2039, p. 28).

Zamecnik's applications invite persons skilled in the art to experiment to determine not only the extent to which the thiophosphate modified nucleotide sequences are likely to resist enzymatic degradation (Claim 17, limitation (c)) but also to determine if, and if so how, those sequences can effect HTLV-III replication and/or gene expression in a host (Claim 17, limitation (a) in combination with limitation (b)). We note that the modifications to the phosphate backbones of the complementary oligonucleotides, which Miller and Ts'O describe in U.S. 4,511,713, published April 16, 1985 (Goodchild Exh. 1028), as suitable for controlling or interfering with the effect or function of foreign nucleic acid in the presence of otherwise normal living cells, produce and seemingly must produce, non-ionic oligonucleotides (Goodchild Exh. 1028, U.S. 4,511,713, col. 1, l. 16-20; col. 2, l. 39-68; col. 4, l. 50-68; and col. 24, Claims 1-5). However, phosphorothioates of Goodchild's claimed invention are ionic oligonucleotides, the utility of which was at that time questionable. See page 28 of Zamecnik's NIH Grant Application. Zamecnik proposes to answer questions regarding the solubilities of the charged phosphorothioates and whether they have suitable cell-uptake capacities for practical application against HTLV-III infection (Claim 17, limitation (b)) by experimentation costing $252,737 (Zamecnik's NIH Grant

Application (Cohen Exh. 2039, p. 4). We find this research proposal to be clear evidence that such experimentation is not merely routine confirmation of an expected result. This finding is strengthened by Goodchild Application 07/071,894, filed July 10, 1987 (Cohen Exh.2016, p. 13, l. 12-16), and PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010, p. 13, 4-8), which state, "If the desired effect is increased uptake of the oligonucleotide into infected cells, modification of the oligonucleotide by addition of a lipophilic group at the 5' end would be beneficial." However, ionic groups, such as phosphorothioates, are not lipophilic. Therefore, the invention defined by Goodchild's Claims 44-46, 48-52, 54-56, 58 and 64 corresponding to Count 1 are neither adequately described in, nor enabled by, Goodchild's disclosure in PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010) or Application 07/071,894, filed July 10, 1987 (Cohen Exh.2016), as required by 35 U.S.C. § 112, first paragraph.

Thus, we conclude that Cohen's U.S. Patent 5,276,019, filed February 22, 1988, is prior art under 35 U.S.C. § 102(e) to the invention defined by Goodchild's Claims 44-46, 48-52, 54-56, 58 and 64 presently designated as corresponding to Count 1 which are, at best, entitled to the February 26, 1988, filing date of Goodchild's Application 07/160,574.

Additionally, we have searched the specifications in Goodchild's Application 07/071,894, filed July 10, 1987 (Cohen Exh. 2016), and PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010), for a written description and enabling disclosure of other phosphate modifications within the full scope of the broader invention of Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270, upon which more limited Claims 44-46, 48-52, 54-56, 58 and 64 depend. Claim 17 is directed to "[a]n oligonucleotide consisting of a nucleotide sequence of 14 to 50 nucleotides complementary to a region RNA or DNA of HTLV-III . . . wherein one to all internal phosphate groups of said oligonucleotide are modified such that the modified phosphate groups do not prevent (a) inhibition of HTLV-III replication, gene expression or both, (b) uptake into infected cells, (c) inhibition of degradation of the oligonucleotide, (d) prevention of the use of the oligonucleotide as a primer by reverse transcriptase, or (e) any combination thereof" (Paper No. 10; emphasis added). Since Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270 encompass the invention of, and are further limited by, Claims 44-46, 48-52, 54-56, 58 and 64, we find that neither Goodchild's Application 07/071,894, filed July 10, 1987 (Cohen Exh. 2016), nor PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010), can

adequately describe the full scope of the generically claimed subject matter for the same reasons we found that neither adequately describes, and concluded that neither reasonably would have enabled the phosphorothioate invention of Claims 44-46, 48-52, 54-56, 58 and 64 encompassed thereby. However, the general disclosure in Goodchild's Application 07/071,894, filed July 10, 1987 (Cohen Exh. 2016), and PCT/US87/01211, filed May 22, 1987 (Goodchild Exh. 1010), further denies that the full scope of the inventions of any of Goodchild's claims designated as corresponding to Count 1 are described and would have been enabled under 35 U.S.C. § 112, first paragraph.

Both applications specifically teach that a "modification known to inhibit nuclease digestion is the replacement of internucleoside phosphate by thiophosphate," cite "Matzura H. and F. Eckstein, European Journal of Biochemistry, 3:448 (1968)" in support thereof, and on that basis, conclude that "some or all of the phosphates in an oligonucleotide sequence can be replaced by thiophosphate to suppress nucleolytic degradation" (Goodchild Exh. 1010, p. 14, ll. 26-32; Cohen Exh. 2016, p. 15, ll. 1-7). For the reasons given with respect to Goodchild's Claims 44-46, 48-52, 54-56, 58 and 64, presently designated as corresponding to Count 1, to the extent the earlier specifications contemplate, and Claims 17-19, 21-25, 27 and 61 designated as corresponding to

Count 1 encompass, complementary oligonucleotides modified by replacing the phosphates in an oligonucleotide sequence thereof by thiophosphate to suppress nucleolytic degradation, neither specification recognizes that the sulfur-modified phosphate groups "do not prevent (a) inhibition of HTLV-III replication, gene expression or both, (b) uptake into infected cells, (c) inhibition of degradation of the oligonucleotide, (d) prevention of the use of the oligonucleotide as a primer by reverse transcriptase, or (e) any combination thereof" (Claim 17; emphasis added) or enable one skilled in the art reasonably to predict those and other benefits necessary for practical utility within a living cell for the full scope of complementary nucleotide sequences claimed wherein any number from one to all of its internal phosphate groups thereof are replaced by a phosphorothioate.

Both of the earlier specifications teach that the "[o]ligonucleotides to be used can be modified at a variety of locations along their length" (Cohen Exh. 2016, p. 12, ll. 24-25; Goodchild Exh. 1010, p. 12, ll. 14-15), including the "internal phosphate groups" (Cohen Exh. 2016, p. 12, l. 28; Goodchild Exh. 1010, p. 12, l. 18). However, both specification state (Cohen Exh. 2016, p. 12, l. 29, to p. 13, l. 3; Goodchild Exh. 1010, p. 12, ll. 19-27; emphasis added):

> Whether oligonucleotides to be used are modified and, if so, the location of the modification(s)[,] will be determined, for example, by the desired effect on viral activity (e.g., inhibition of viral replication, gene expression or both), uptake into infected cells, inhibition of degradation of the oligonucleotides once they are inside cells, and prevention of their use as a primer by reverse transcriptase.

This statement appears to invite to experimentation rather than to provide the requisite guidance, direction and specificity necessary to describe a useful invention and enable persons skilled in the art to make and use it without undue experimentation.

Interestingly, both earlier applications provide the following specific instruction (Cohen Exh. 2016, p. 14, ll. 20-32; Goodchild Exh. 1010, p. 14, ll. 12-25):

> It has now been demonstrated that 3' or 5' exonucleases, such as phosphodiesterases from snake venom or spleen, can progress past a single methylphosphonate internucleoside linkage. It has also been shown that two such linkages in succession constitute a strong block to the enzyme's activity and can increase the half life of the oligomer in the presence of such an enzyme by 100 fold. Good protection from destruction of an oligodeoxynucleotide by exonucleases can be afforded by using methylphosphonate linkages at the last two positions at each end of the molecule. This enhances the survival of the compound in vivo.

We are at a loss to understand why this particular teaching establishes that the full scope of any of the inventions encompassed by Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270 designated as corresponding to Count 1 are

patentable to Goodchild. While Miller and Ts'o (Miller), U.S. Patent 4,511,713 (Goodchild Exh. 1028), issued April 16, 1985, is prior art under 35 U.S.C. § 102(b) to all of Goodchild's claims corresponding to Count 1 and thus information available to persons skilled in the art reading Goodchild's applications, Miller's teaching is limited to a very specifically modified nonionic deoxyribooligonucleosides complementary to foreign nucleotide sequences of viruses in general. Miller reported that methylphosphonates were useful to hinder replication and gene expression of viruses in mammals. We shall hereafter consider the substance and scope of Miller's prior art disclosure in depth (Section 8A, infra). For the present purpose of determining whether Cohen's '019 patent stands as a bar to Goodchild's claims, we hold that Goodchild's claims are not entitled to benefit of 35 U.S.C. §§ 119 or 120 of its patented Application 06/867,231, filed May 23, 1986, its PCT/US87/01211, filed May 22, 1987, or its Application 07/071,894, filed July 10, 1987.

5. Is Cohen's '019 patent entitled to its claim under § 120?

Even if we were to grant Goodchild's claims corresponding to Count 1 benefit of the May 22, 1987, filing date of PCT/US87/01211, Cohen's U.S. 5,276,019, filed February 22, 1988, claims benefit under 35 U.S.C. § 120 of the March 25, 1987, filing date of Cohen's Application 07/030,073 (Cohen Exh. 2014).

In its Decision on Preliminary Motions and Order (Paper No. 104), the Board denied Cohen's claims under 35 U.S.C. § 120 for benefit of the March 25, 1987, filing date of Cohen's Application 07/030,073 (Cohen Exh. 2014) for Claims 1-5, 8-16, 19-32, 34, 37 and 39-48 of Cohen's '423 patent (Paper No. 104, pp. 25, first para., and p. 32, l. 10-15). However, even though the Board recognized that the scope and content of the oligonucleotides of the invention defined by the claims in Cohen's '423 patent designated as corresponding to Count 1 were far broader in scope and content of the oligonucleotides there claimed than the scope and content of the oligonucleotides of the invention defined by the claims in Cohen's '019 patent designated as corresponding to Count 1, nevertheless the Board denied the claim in Cohen's '019 patent for benefit under 35 U.S.C. § 120 of the March 25, 1987, filing date of Cohen's Application 07/030,073 (Cohen Exh. 2014) "for the reasons" it denied Cohen's claim for benefit under 35 U.S.C. § 120 of the March 25, 1987, filing date of Cohen's Application 07/030,073 (Cohen Exh. 2014) in Cohen's '423 patent (Paper No. 104, pp. 56-57).

We should not use tenuous procedural grounds to excuse ourselves from our duty to find facts. We therefore shall consider the merits of Cohen's claims for benefit under 35 U.S.C. § 120 and compare the subject matter claimed in Cohen's '019

patent to the subject matter described in Cohen's Application 07/030,073, filed March 25, 1987.

The formula of Claims 1, 23 and 35 of Cohen's '019 patent depicting modified oligonucleotide compounds useful in compositions and methods for "inhibiting the replication or cytopathic effect of a foreign nucleic acid in a host" (Claims 1, 23 and 35), is identical in structure and specified utility to Formula I described in the paragraph bridging pages 1 and 2 of Application 07/030,073 (Cohen's '073 application), filed March 25, 1987, but for the definitions of "X" and "n" in each. In the formula of independent Claims 1, 23 and 35 of Cohen's '019 patent, "n is in the range of from 2 to 30, inclusive" and "X is selected from the group consisting of S and O such that at least one X is S" (Goodchild Exh. 1014, cols. 17, 19 and 20). In representative dependent Claims 2(1), 24(23) and 36(35) of Cohen's '019 patent, "n is in the range of 14 to 30, inclusive" (Goodchild Exh. 1014, cols. 18-20). In representative dependent Claims 3(2), 25(24) and 37(36) of Cohen's '019 patent, "greater than 95% of X are S" (Goodchild Exh. 1014, cols. 18-20). In representative dependent Claims 4(3), 26(25) and 38(37) of Cohen's '019 patent, "X is S" (Goodchild Exh. 1014, cols. 18-20).

Formula I of Cohen's '073 application is depicted on page 1 thereof (Cohen Exh. 2014, p. 1). In Formula I of Cohen's '073

application, compounds wherein "n is equal to 15-30" and "X" is "S- Phosphorothioate" are preferred (Cohen Exh. 2014, p. 1). In Formula I of the methods of using and providing compounds of Formula I of Claims 1 and 20 of Cohen's '073 application to inhibit the replication and cytopathic effect of foreign nucleic acid in cells, X is replaced by "S" and "n = 2-30" (Cohen Exh. 2014, pp. 12 and 14-15). Claim 7 of Cohen's '073 application broadly defines foreign nucleic acid replication-inhibiting phosphorothioates as "phosphorothioate oligo deoxyribonucleotide[s]" (Cohen Exh. 2014, p. 13).

The specification of Cohen's '073 application expressly states:

> Phosphorothioates are compounds in which one of the non-bridging oxygen atoms in the phosphate portion of the nucleotide is replaced by sulfur. [Cohen Exh. 2014, first sentence of paragraph bridging pp. 3-4.]
>
> Finally, the method can be applied to "mixed linkage" analogues having phosphorothioate and, in the same molecule, other types of backbone modifications, such as methyl phosphonates and phosphorotriesters. [Cohen Exh. 2014, second to last sentence of paragraph bridging pp. 3-4.]
>
> For the biological tests, a sequence (S-ODN-1), the phosphorothioate oligodeoxynucleotide was selected which is an anti-sense counterpart to the nucleotide sequence existing in tat-III and art/trs genes of HIV, as these genes are essential for viral replication. Also, selected was a sequence (S-ODN-2) which is complementary to the sequence at the initiation site of tat-III. [Cohen Exh. 2014, first three sentences of paragraph bridging pp. 5-6.]
>
> Table 1 contains a list of the test compounds which

> were synthesized. Each of the compounds was given a trivial name for the convenience of discussion, and has the molecular structure indicated by the conventional nomenclature for polynucleotides, with the exception that each internucleotide linkage indicated by subscript "s" is an Rp, Sp-phosphorothioate, wherein the average sulphur content is >95%, as judged by ^{31}P NMR analysis.
>
> It was found that longer oligos had more potent effects, and that oligo-dC phosphorothioate had more potency than oligo-dA phosphorothioates on the basis of molarity of the compounds. Therefore, the binding of the oligos to the relevant polynucleotide site(s) of the virus leads to protection against HIV cytopathic effects. [Cohen Exh. 2014, first two full paragraphs on p. 7 (emphasis added).]

In Table 1 of Cohen's '073 application, there is described at least one 14 mer compound of Claims 3, 4, 16, 17, 18, 19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's '019 patent which was shown to have protected ATH8 cells from HTLV-III (Cohen Exh. 2014, p. 8, Table 1; pp. 9-11):

Trivial Name	Sequence (5'-3') of Phosphorothioate Analogues of Oligodeoyribonucleotides
S-ODN-1	d-($T_sC_sG_sT_sC_sG_sC_sT_sG_sT_sC_sT_sC_sC$)

. . . . .

> S-ODN (phosphorothioate analogue-d) = oligodeoxy-nucleotides or phosphorothioates wherein dA and dC are compounds of Formula I.

Based on the above-cited information in Cohen's '073 application, we find that the full scope of the invention of Claims 3, 4, 16, 17, 18, 19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's '019 patent is described in Cohen's '073

application in compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. Based on the above-cite information in Cohen's '073 application, we conclude that any person skilled in the art would have been enabled to make and use the full scope of the invention of Claims 3, 4, 16, 17, 18, 19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's '019 patent without undue experimentation as required under 35 U.S.C. § 112, first paragraph. Accordingly, Cohen has perfected its claim for benefit under 35 U.S.C. § 120 of the March 25, 1987, filing date of Cohen's Application 07/030,073 at least for the full scope of Claims 3, 4, 16, 17, 18, 19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's U.S. 5,276,019. We need not decide whether the remaining broader claims of Cohen's '019 patent are entitled to benefit under 35 U.S.C. § 120 of the filing date of Cohen's '073 application.

6. Does Goodchild's '463 patent bar Cohen's '019 patent claims?

Goodchild's U.S. Patent 4,806,463 issued February 21, 1989, from Application 06/867,231, filed May 23, 1986. Even if we assume that the earliest date to which any one of Claims 1-48 of Cohen's U.S. 5,264,423, Claims 1-43 of Cohen's U.S. 5,276,019, and Claims 1-20 of Cohen's U.S. 5,286,717 are entitled under 35 U.S.C. § 120 is the February 22, 1988, filing date of Cohen's

Application 07/159,017,[9] conclusions that Goodchild's patent is prior art under 35 U.S.C. § 102(b) as to the subject matter defined by Cohen's claims designated as corresponding to Count 1 (Paper No. 104, p. 10, first para., last sentence; p. 25, first para.; p. 25, second para., first sentence; p. 32, last sentence of para. bridging pp. 32-33) and bars consideration of evidence Cohen filed under 37 CFR § 1.131 (Paper No. 104, p. 36, last paragraph) cannot withstand scrutiny. 35 U.S.C. § 102(b) reads:

> A person shall be entitled to a patent unless-
>
> . . . . .
>
> (b) the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States . . . .

Goodchild's U.S. Patent 4,806,463, issued February 21, 1989. Thus, the Goodchild patent was issued long after the

---

[9] In Table 2 and Figures 5A and 5B of Cohen's '019 patent, there is described at least two 14 mer compounds of Claims 3, 4, 16, 17, 18, 19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's '019 patent which are there shown to exhibit anti-HIV activity in ATH8 cells and low cytotoxicity (Goodchild Exh. 1014, col. 10, Table 2; Figs. 5A & 5B):

Trivial Name	Sequence (5'-3') of Phosphorothioate Analogues of Oligodeoyribonucleotides
S-ODN-1	d-($T_sC_sG_sT_sC_sG_sC_sT_sG_sT_sC_sT_sC_sC$)
S-ODN-3	d-($C_sA_sT_sA_sG_sG_sA_sG_sA_sT_sG_sC_sC_sT$)

S-ODN-3 in Table 2 of Cohen's '019 patent appears to correspond to S-ODN-4 in Table 1 of Cohen's '073 application.

February 22, 1988, filing date of Cohen's 07/159,017 application, from which Cohen's '019 patent directly issued, and Cohen's '423 and '717 patents issued respectively as a continuation and a division thereof. Thus, Goodchild's patent is not prior art under 35 U.S.C. § 102(b) to any of Cohen's claims directed exclusively to subject matter adequately described in, and enabled by, either Cohen's Application 07/159,017, filed February 22, 1988, or Cohen's Application 07/030,073, filed March 25, 1987, and cannot bar consideration of secondary evidence with respect to those claims.

Cohen filed its Application 07/159,017 on February 22, 1988, as a continuation-in-part of Cohen's Application 07/030,073, filed March 25, 1987. Accordingly, Cohen's Application 07/159,017 presumably describes subject matter which is new to Cohen's Application 07/030,073. Thus, to the extent the Board limited its search for an adequate written description of subject matter defined by Cohen's claims designated as corresponding to Count 1 to Cohen's Application 07/030,073, the Board was remiss.

While it is true that, under appropriate circumstances, the Board may consider the parties' claims commensurate in scope to the parties' arguments, no claim for benefit under 35 U.S.C. §§ 120 and 119 of the filing date of an earlier filed application should be disregarded as a matter of procedural convenience.

Independently claimed subject matter and dependently claimed subject matter of more limited scope may not, and here should not, stand or fall together.

We also note that the formula of original Claims 1 and 5 of Cohen's Application 07/159,017, including respective definitions where "n is an integer of from 2 to 30 and X is selected from the group consisting of S and O, with the provision that at least one X in the compound is S" (Claim 1) and "n is 2-30 and X is O or S, wherein at least one X is S" (Claim 5), is identical to the formula, and substantially identical to the definitions of "n" and "X" of independent Claims 1, 23 and 35 of Cohen's U.S. Patent 5,276,019, which issued January 4, 1994. Moreover, original Claims 6, 7 and 8 of Cohen's Application 07/159,017 read:

> 6. The composition of claim 5 wherein there are two monomers wherein X is S and the remaining monomers are such that X is O.
>
> 7. The composition of claim 6 wherein the polymer is end-capped with monomers wherein X is S and the remaining monomers are such that X is O.
>
> 8. The composition of claim 5 wherein the monomers are present in equal amounts.

See also the Summary of the Invention of Cohen's U.S. 5,276,019 (Goodchild Exh. 1014, col. 3, l. 45, to col. 5, l. 48; especially col. 4, l. 30-53).

Accordingly, we conclude that Goodchild's U.S. 4,806,463,

issued February 21, 1989, is available as prior art with respect to Claims 1-43 of Cohen's U.S. 5,266,019 under 35 U.S.C. § 102(e), but it is not prior art with respect to Claims 1-43 of Cohen's U.S. Patent 5,266,019 under 35 U.S.C. § 102(b). Hence, whether or not the Board properly declined to consider Cohen's showing under 37 CFR § 1.131 with regard to Claims 1-48 of Cohen's '423 patent (Paper No. 104, p. 36, last full para.), it should not bar a showing by Cohen under 37 CFR § 1.131 with regard to subject matter claimed in Cohen's '019 patent.

7. Cohen's showing under 37 CFR § 1.131

We proceed to determine whether the Declaration of Jack Cohen et al. under 37 CFR § 1.131 for Cohen's U.S. 5,264,423 (Cohen Exh. 2046) should have been considered with regard to Claims 1-43 of Cohen's U.S. 5,276,019. The Board granted in-part Goodchild's Preliminary Motion 2 (Paper No. 33) and Goodchild's Preliminary Motion 5 (Paper No. 37) respectively "for reasons set forth with respect to Goodchild's Preliminary Motion 1" (Paper No. 104, p. 56-57, bridging para., last sentence) and "for reasons set forth above for Goodchild's Preliminary Motion 4" (Paper No. 104, p. 75, first para., last two lines). Regarding the claims in Cohen's '019 patent, the Board said (Paper No. 104, p. 57/p. 75-76, bridging para.):

> The[/the] only difference between the claims in the

> '019 patent and the '423 patent is that the claims in the former[/'019] patent are narrower in scope as[/since] they are directed to compounds which have a nucleotide sequence which is complementary[/a complementary base sequence] with a portion of a foreign nucleic acid wherein "X" is selected from the group consisting of "S and O such that at least one X is S."

The Board seems here to have misapprehended the significance of many of the claims in Cohen's '019 and '423 patents and the differences in scope between the claims in Cohen's '019 and '423 patents. Having overlooked the different scope of the claims in Cohen's '019 patent and reconsidered Cohen's claim therein for benefit under 35 U.S.C. § 120 in that light, we find that the Board appears to have unwittingly barred consideration of any showing by Cohen under 37 CFR § 1.131 for claims in Cohen's '019 patent because, on consideration of the broader scope of subject matter claimed in Cohen's '423 patent, it agreed with Goodchild that (Paper No. 104, p. 36, last para.):

> [A] declaration pursuant to 37 C.F.R. § 1.131 can not be used to antedate a "§ 102(b)" reference. That is, a reference which was publicly available more than one year prior to an applicant's filing date, cannot be overcome by a declaration of prior reduction to practice because such a reference is a statutory bar under § 102(b).

While the statement of law may be correct, neither Goodchild's U.S. 4,806,463, patented February 21, 1989, nor Zamecnik's NIH Grant Application (Goodchild Exh. 1015), found to have been first made available to the public on September 30,

1986 (Paper No. 104, p. 62, first para.), bar consideration of the evidence Cohen filed under 37 CFR § 1.131 because Goodchild's '463 patent was not patented more than one year prior to the February 22, 1988, filing date of Cohen's Application 07/159,017 and Zamecnik's Grant Application was not described in a printed publication in this or a foreign country more than one year prior to the March 25, 1987, filing date accorded Claims 3, 4, 16, 17, 18, 19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's U.S. 5,266,019. See 35 U.S.C. § 102(b).

Cohen labeled its Declaration under 37 CFR § 1.131 "for U.S. 5,264,423" (Cohen Exh. 2046). As a result, the Board considered the evidence Cohen submitted to antedate Goodchild's patent and Zamecnik's NIH Grant Application primarily for subject matter claimed in Cohen's '423 patent. For the subject matter claimed in Cohen's '423 patent, Goodchild's patent and Zamecnik's NIH Grant Application were determined to be prior art under 35 U.S.C. § 102(b) and bar Cohen's showing under 37 CFR § 1.131. However, Cohen's showing is not barred to the extent subject matter claimed in Cohen's '019 patent is entitled to benefit under 35 U.S.C. § 120 of the March 25, 1987, filing date of Cohen's Application 07/030,073. We have determined (Section 5, supra) that Claims 3, 4, 16-19, 21, 22, 25, 26, 33, 34, 37, 38, 42 and 43 of Cohen's '019 patent are entitled to benefit under

35 U.S.C. § 120 of the March 25, 1987, filing date of Cohen's Application 07/030,073. Nevertheless, we defer consideration of Cohen's Declaration under 37 CFR § 1.131 until final hearing because the issue may be moot. On reconsideration, we withdraw our grants of, and defer for further consideration, Goodchild's Preliminary Motions 1, 2, 4 and 5 under 37 CFR § 1.633(a) for judgment as to the patentability of subject matter Cohen claims under 35 U.S.C. § 103 in view of prior art including Goodchild's patent and Zamecnik's NIH Grant Application.

8. Patentability of the parties' claims corresponding to Count 1 over prior art

A. Goodchild's claims corresponding to Count 1

We proceed to consider the patentability of Claims 17-19, 21-25, 27, 44-46, 48-52, 54-56, 58, 61 and 64 of Goodchild's Application 08/346,270 over prior art of record. We were not previously asked to do so. As determined supra, Goodchild's '270 application is entitled, at the earliest, to benefit of continuation-in-part Application 07/160,574 filed February 26, 1988. Accordingly::

> Cohen's '019 patent (Goodchild's Exh. 1014) filed February 22, 1988, is prior art under 35 U.S.C. § 102(e) to all Goodchild's claims corresponding to Count 1;
>
> Zamecnik's June '86 article (Cohen Exh. 2030) is prior art under 35 U.S.C. § 102(b) to all Goodchild's claims corresponding to Count 1;

Matsukura et al. (Matsukura's '87 article), "Phosphorothioate analogs of oligdeoxynucleotides: Inhibitors of replication and cytopathic effects of human immunodeficiency virus," Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 7706-7710 (Nov. 1987)(Cohen Exh. 2031), is prior art under 35 U.S.C. § 102(a) to all Goodchild's claims corresponding to Count 1;

and

Zamecnik's Grant Application, published September 30, 1986 (Cohen Exh. 2039), is prior art under 35 U.S.C. § 102(b) to all Goodchild's claims corresponding to Count 1.

First, the same patentable invention as Goodchild's claims corresponding to Count 1 is described, claimed, taught, and exemplified by Cohen's '019 patent. Goodchild's claims corresponding to Count 1 are prima facie unpatentable under 35 U.S.C. § 102(e) and/or 35 U.S.C. § 103 thereover.

Second, at least one synthetic oligonucleotide encompassed by each of Goodchild's claims corresponding to Count 1 is described, taught, and exemplified in Matsukura's '87 article (Cohen Exh. 2031). Goodchild's claims corresponding to Count 1 are prima facie unpatentable under 35 U.S.C. § 102(a) and/or 35 U.S.C. § 103 thereover.[10]

Third, Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270, filed November 23, 1994, are prima facie

---

[10] The disclosure of Matsukura's November 1987 article (Cohen Exh. 2031) is cumulative to the disclosure of Cohen's '019 patent and need not be separately considered.

unpatentable under 35 U.S.C. § 103 in view of the combined teachings of Miller et al. (Miller), U.S. Patent 4,511,713, patented April 16, 1985 (Goodchild's Exh. 1028); Smith et al. (Smith), "Antiviral effect of an oligo(nucleoside methylphosponate) complementary to the splice junction of herpes simplex virus type 1 immediate early pre-mRNAs 4 and 5," Proc. Natl. Acad. Sci. USA, Vol. 83, pp. 2787-2791 (May 1986)(Cohen Exh. 2135); and either Goodchild's acknowledgment of the state of the art in Goodchild et al., U.S. 4,806,463 (Goodchild's Exh. 1002, col. 1, l. 6-53; and col. 2, l. 50, to col. 3, 20), including the Figure and statement that "[t]he primary nucleotide sequence of the HTLV-III/LAV genome has been determined by several groups of investigators" (Goodchild's Exh. 1002, col. 2, l. 50-63), or the teaching of Zamecnik et al. (Zamecnik's '86 article), "Inhibition of replication and expression of human T-cell lymphotropic virus type III in cultured cells by exogenous synthetic oligonucleotides complementary to viral RNA," Proc. Natl. Acad. Sci. USA, Vol. 83, pp. 4143-4146 (June 1986) (Cohen Exh. 2030). Goodchild first mentioned methylphosphonates as internucleoside-modified oligonucleosides complementary to RNA or DNA of HTLV-III at page 14, lines 13-25, of PCT/US87/01211 filed May 22, 1987 (Goodchild Exh. 1010, p. 14, l. 13-25). However, we have concluded that Goodchild would have first

enabled persons skilled in the art to make and use the full scope of the Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270 designated as corresponding to Count 1 no earlier than February 26, 1988 (Section 4, supra). Accordingly, the Smith and Zamecnik's '86 article articles are prior art under 35 U.S.C. § 102(b) to Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270, filed November 23, 1994.

In Miller's Broad Description of the Invention (Goodchild's Exh. 1028, col. 2, l. 50, to col. 3, l. 48), Miller discloses:

> [A] method which involves the determination of the relevant sequence or sequences of any foreign nucleic acid in or adjacent to an otherwise normal mammalian cell and this sequence or sequences will be bound or interfered with by a nonionic deoxyribooligonucleoside alkyl- or arylphosphonate analogue . . . preferably a methylphosphonate, which possess a nucleic acid base sequence complementary to the indicated foreign nucleic acid sequence or sequences. These nonionic, complementary oligonucleotide analogs will be synthesized specifically and consequently serve to bind the foreign nucleic acid into an essentially inactive state so that it cannot replicate itself and/or function in an undesired manner . . . .
>
> The oligonucleoside methylphosphonates . . . are specifically designed to have the following unique properties: (1) they can easily pass through the membranes of living cells and can enter the cell's interior; (2) they are resistant to degradation or hydrolysis by nuclease enzymes found within the cells, and thus have a relatively long lifetime within the cell; and (3) they can strongly interact with complementary nucleic acids or polynucleotides found inside the cell to form stable complexes therewith. By interacting with a selected complementary foreign nucleic acid in a cell or adjacent to a cell whether the nucleic acid is derived from bacteria, virus or malfunction, the phosphonate can selectively inhibit the function or

> expression of that particular nucleic acid without disturbing the function or expression of other nucleic acids present in the cell. This selectivity potentially allows one to prevent the growth of viruses, bacterial cells, transformed cells, pathological cells or tumor cells in the presence of normal, healthy cells. . . . [T]he invention contemplates the use of the indicated alkyl . . . the single stranded regions of predetermined foreign nucleic acid sequences and thereby inhibit the function or expression of the foreign nucleic acid involved. Because of the unique selectivity of the analogues, based on sequence complementary, the normal functioning of the cell is not affected. Each virus, bacteria, and malfunctioning cellular nucleic acid has its own distinctive "fingerprint" nucleic acid sequence. Hence, once this sequence is determined over a reasonable length of the foreign nucleic acid chain, it is possible to prepare its complementary phosphonate analogue which then binds itself to the foreign nucleic acid and prevents it from replicating, directing protein synthesis and/or otherwise functioning in an undesirable manner. . . .[I]t is believed . . . that an analogue which is complementary with respect to a 3-20, preferably 9-12, base sequence of the foreign nucleic acid will usually be adequate to effectively control or interfere with the foreign nucleic acid.

Miller explains that "sequences for some viral, bacterial and mammalian cellular nucleic acids are already well established" and need not be determined (Goodchild's Exh. 1028, col. 4, l. 64-68). Miller adds (Goodchild's Exh. 1028, col. 5, l. 5-9):

> [G]enerally speaking, it may be preferable to utilize a sequence at or near the 5' end of the chain or the middle thereof rather than the end as related to the function of the foreign nucleic acid in replication, expression, or translation processes.

Goodchild teaches that the primary nucleotide sequence of the HTLV-III genome was known to persons having ordinary skill in

the art at the time Goodchild's patent application was filed on May 23, 1986 (Goodchild's Exh. 1002, col. 2, l. 50-63). Zamecnik's '86 article also teaches that "[t]he primary nucleotide sequence of the HTLV-III genome has been determined during the past year by several groups of investigators" (Cohen Exh. 2030, p. 4144, col. 2, second full para.). Zamecnik "show[s] that complementary synthetic oligodeoxynucleotides directed toward different regions of the HTLV-III genome inhibit virus replication and gene expression in cultured HTLV-III-transformed human lymphocytes" (Cohen Exh. 2030, p. 4143, col. 2, first para.).

Zamecnik found (Cohen Exh. 2030, p. 4143, col. 2, first para.):

> [T]he primary nucleotide sequences of the primer area and certain other parts of the HTLV-III genome are highly conserved.

In that light, Zamecnik chose, inter alia, as the "highest-priority oligonucleotide competitive inhibition targets . . . (iii) sequences from the splice sites of the pre-mRNA that expresses the 3' open reading frame region (Cf. Refs. 25 and 26 [i.e., Sodroski, et al., J. Virol., Vol. 55, pp. 831-835 (1985), and Wong-Staal, et al., Nature (London), Vol. 317, pp. 395-403 (1985)])" (Cohen Exh. 2030, p. 4144, col. 2, second full para.). More specifically, Zamecnik stated (Cohen Exh. 2030,

p. 4144, col. 2, bottom):

> We . . . tested a sequence complementary to a splice donor site from the 3' open reading frame region and one complementary to a splice acceptor site. The results of these tests are shown in Table 1.
>
> The greatest inhibition occurred with the sequence ACACCCAATTCTGAAATGG, complementary to the splice acceptor site.

With regard to the ACACCCAATTCTGAAATGG sequence and the associated splice acceptor site, the footnote to the splice acceptor site reads (Cohen Exh. 2030, p. 4145, Table 1, last footnote):

> Computer search of all known sequences did not reveal any similar 20-nucleotide sequence with fewer than seven mismatches. This is the splice acceptor site for the tat-III gene (35).

Reference "(35)", which is cited as the source of the splice acceptor site for the tat-III gene is Arya, et al., Science, Vol. 229, pp. 69-73 (1985), which is prior art to all Goodchild's claims corresponding to Count 1.

Zamecnik also found:

> [I]nhibition of viral replication by exogenous oligodeoxynucleotides appears to depend upon uptake of sufficient amounts by the cells. [Cohen Exh. 2030, p. 4144, col. 2, l. 1-3;]
>
> [A] large fraction of oligodeoxynucleotide . . . is unaccounted for, being either degraded or incorporated into macromolecules. [Cohen Exh. 2030, p. 4144, col. 2, first full para.; and]

> Terminally labled oligodeoxynucleotides disappear more rapidly than those labeled internally. [Cohen Exh. 2030, p. 4144, col. 2, first full para.;]

Zamecnik acknowledged Miller and collaborators for their work using oligodeoxynucleotides modified as the methylphosphonates to inhibit herpes virus replication and cited, inter alia, the Smith article [Cohen Exh. 2030, p. 4143, col. 2, first para.] as an example of their work. Finally, Zamecnik concluded [Cohen Exh. 2030, p. 4146, col. 1, first full para.]:

> The present studies point to the potential usefulness of synthetic oligonucleotides in the treatment of patients with AIDS and ARC. The potential problem of nuclease degradation of the oligonucleotides may conceivably be overcome, by daily intravenous administration, or by internucleotide phosphate and other modifications of oligomers.

Smith teaches (Cohen Exh. 2035, p. 2787, col. 1, second para., to the end of col. 2, bridging para.; citations omitted):

> An alternative approach to antiviral chemotherapy is the use of sequence-specific oligonucleotides or their analogues to selectively inhibit viral gene expression at the level of mRNA processing or translation. For this purpose we have developed sequence-specific nonionic nucleic acid analogues that contain a 3'-5' methylphosphonate group in place of the negatively charged phosphodiester group normally found in oligonucleotides . . . . These analogues are resistant to nuclease hydrolysis and penetrate mammalian cells in culture . . . .
>
> To explore the possibility that control of gene expression by methylphosphonates could be effective antiviral modality, we synthesized an oligo(nucleoside methylphosphonate) [d(TpCCTCCTG; deoxynucleoside methylphosphonate residues . . . [underlined]] that is complementary to the acceptor splice junction of herpes simplex virus type 1 (HSV-1) immediate early (IE)

> mRNAs 4 and 5 . . . . The rationale for this choice is based on previous findings indicating that . . . (iii) RNA splicing may be involved in the control of gene expression (12, 13).

Smith's data indicates that "d(TpCCTCCTG) penetrates rapidly into the cells and exerts an inhibitory effect very early in the virus replicative cycle" (Cohen Exh. 2135, p. 2788, col. 2, third para., last sentence) and that the "inhibitory effect is sequence-specific . . ." (Cohen Exh. 2135, p. 2789, col. 1, first full para., first sentence). Smith provided the following explanation for selecting the target sequence (Cohen Exh. 2135, p. 2790, col. 1-2, bridging para.; citations omitted; emphasis added):

> In this report, we describe the results of our studies with an eight-residue oligomer [d(TpCCTCCTG)] that is complementary to the acceptor splice junction of HSV-1 IE mRNAs 4 and 5 (Fig. 1). Considerations leading to its selection include previous findings indicating that (i) HSV-1 IE genes . . . play a regulatory role in virus growth and (ii) RNA splicing may be involved in the control of gene expression . . . .

According to Smith, the data indicate that there is "little, if any deleterious effect on host-cell macromolecular metabolism and growth rate" (Cohen Exh. 2135, p. 2790, cols. 1-2, bridging para., last sentence), "HSV-1 replication is inhibited by d(TpCCTCCTG) in a dose-dependent fashion . . . [, and the] inhibitory effect is almost immediate" (Cohen Exh. 2135, p. 2790, col. 2, first para.). However, Smith refused to jump to

conclusions (Cohen Exh. 2135, p. 2790-91, bridging para.):

> It is tempting to speculate that the effect of d(TpCCTCCTG) on virus growth is mediated by its ability to interfere with the spicing of IE pre-mRNA 4 and 5, thereby inhibiting the synthesis of the respecting proteins . . . . However, in the absence of direct evidence that d(TpCCTCCTG) interferes with IE mRNA processing, such conclusions are premature.

Nevertheless, Smith confidently concluded (Cohen Exh. 2135, p. 2791, col. 1, first full para.):

> [O]ur data are consistent with the interpretation that these IE genes play a significant role in the control of virus growth. The oligomer inhibits (or significantly reduces) the synthesis of all viral proteins, while primarily reducing the synthesis of only low molecular weight protein species [in host cells]. . . . [V]iral DNA synthesis is decreased in d(TpCCTCCTG)-treated cells while host-cell DNA synthesis is increased . . . and the inhibitory effect is of d(TpCCTCCTG) . . . appears to be sequence-specific.

Ultimately, based on prior art reports, Smith predicted (Cohen Exh. 2135, p. 2791, col. 1, second full para.; citations omitted; emphasis added):

> It is quite probable that a base sequence that is complementary to a relatively short oligomer such as d(TpCCTCCTG) is relatively common in both viral and cellular genes. . . . [T]he oligomer is complementary to a 6-base sequence in the acceptor splice junction of IE mRNAs 4 and 5 on the HSV-2 genome . . . and it inhibits the growth of HSV-2 almost as well as that of HSV-1 (Fig. 2). A limited computer search has shown that the oligomer is also complementary to a 7-base sequence in the coding region of the mRNA for the L protein of vesicular stomatitis virus and to nucleotides 72-80 in the coding region of rabbit β-globin mRNA. Consistent with these homologies, d(TpCCTCCTG) . . . inhibits (85%) the synthesis of vesicular stomatitis virus in infected

> mouse L. Cells, as well as inhibiting the translations of β-globin mRNA in a cell-free rabbit reticulocyte translation system . . . .

Having considered all the evidence before us, we conclude that subject matter defined by Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270 prima facie would have been obvious to persons having ordinary skill in the art before the date Goodchild first enabled one skilled in the art to make and use the full scope of the subject matter claimed as required by 35 U.S.C. § 103 on February 26, 1988. Persons having ordinary skill in the art would have learned from Miller, U.S. 4,511,713, that nonionic oligonucleotide methylphosphonate analogues having a base sequence complementary to a 3-20 nucleotide sequence selective for replication or gene expression of a specific virus are useful for controlling or interfering with the effect or function of the RNA or DNA of the specific virus in normal living cells. If a 3-20 nucleotide sequence selective for replication or gene expression of the specific virus is unknown or uncatalogued, one must be determined. See Claims 1-5 of Miller. The oligonucleotide methylphosphonates Miller contemplates are (Goodchild Exh. 1028, col. 3, l. 3-12):

> . . . chemically synthesized analogues . . . which are specifically designed to have the following properties: (1) they can easily pass through the membranes of living cells and can enter the cell's interior; (2) they are resistant to degradation or hydrolysis by nuclease enzymes

> found within the cells, and thus have a relatively long lifetime within the cell; and (3) they can strongly interact with complementary nucleic acids or polynucleotides found inside the cell to form stable complexes therewith.

Goodchild, U.S. 4,806,463, acknowledges that the primary nucleotide sequence of the HTLV-III genome was known or catalogued prior to May 23, 1986 (Goodchild Exh. 1002, col. 2, l. 57-65). Zamecnik not only teaches that the primary nucleotide sequence of HTLV-III genome was known prior to June 1986 (Cohen Exh. 2030, p. 4144, col. 2, second full para.), Zamecnik also discloses an unmodified 20 nucleotide sequence complementary to the splice acceptor site for the tat-III gene published in 1985 (Cohen Exh. 2030, p. 4145, Table 1, last footnote) which most selectively inhibits virus replication and gene expression in cultured HTLV-III-transformed human lymphocytes (Cohen Exh. 2030, p. 4144, col. 2, last nine lines).[11]

Smith describes nonionic oligonucleotides consisting of a nucleotide sequence complementary to the acceptor splice junction

---

[11] At page 22, first paragraph, of Zamecnik's NIH Grant Application (Cohen Exh. 2039), there appears the following statement:

> There is also a unique double splice mechanism related to the tat gene of HTLV-III (12, 13).

There cited are (12) E. P. Groody, Doctoral Dissertation, Northwestern University, 1985, and (13) R. L. Letsinger, et al., Tetrahedron, Vol. 40, p. 137 (1984).

of HSV-I immediately early (IE) mRNA. The complementary oligonucleotide was rendered nonionic by replacing the negatively charged phosphodiester groups normally found in oligonucleotides with methylphosponate groups (Cohen Exh. 2135, p. 2787, cols. 1-2). Nonionic complementary oligonucleotides are said to be resistant to nuclease hydrolysis and to penetrate mammalian cells in culture (Cohen Exh. 2135, p. 2787, col. 1, second para.). Smith rationalized using an oligo(nucleoside methylphosphonate) that is complementary to the acceptor splice junction of HSV-I immediately early (IE) mRNA because IE genes were reported to play a regulatory role in virus replication and other publications indicate that RNA splicing may be involved in the control of gene expression (Cohen Exh. 2135, p. 2787, cols. 1-2, bridging para.). Smith reported that the elected nonionic oligo(nucleoside methylphosphonate) complementary to the sequence specific acceptor splice junction of HSV-I immediately early (IE) mRNA "penetrates rapidly into the cells and exerts an inhibitory effect very early in the virus replicative cycle" (Cohen Exh. 2135, p. 2788, col. 2, last full para.). Smith concluded that nonionic oligo(nucleoside methylphosphonate)s complementary to the sequence specific acceptor splice junction of HSV-I immediately early (IE) mRNA utilized selectively inhibit virus growth with little or no deleterious effect on host cell

macromolecular metabolism (Cohen Exh. 2135, p. 2791, col. 2). Finally, Smith predicts (Cohen Exh. 2135, p. 2791, col. 2, last sentence):

> Oligo (nucleoside methylphosphonate)s, properly designed to be complementary to sequences that play key regulatory roles in virus replication, may prove effective in antiviral chemotherapy.

In light of the combined prior art teachings, assuming prior knowledge in the art of the primary nucleotide sequence of HTLV-III and considerable prior art successes using nonionic oligo(nucleoside methylphosphonate)s complementary to the sequence-specific acceptor splice junction of HSV-I immediately early (IE) mRNA, it would have been obvious to persons having ordinary skill in the art to make and use modified nonionic oligo(nucleoside methylphosphonate)s complementary to a known sequence specific acceptor splice site of the tat-III gene of the HTLV-III genome to inhibit replication and gene expression of HTLV-III in mammalian cells without deleterious effects. Accordingly, we conclude that Claims 17-19, 21-25, 27 and 61 of Goodchild's Application 08/346,270, filed November 23, 1994, are unpatentable under 35 U.S.C. § 103 in view of the combined prior art teachings of Miller and Smith, optionally further in view of either Zamecnik's '86 article or prior knowledge in the art of the primary sequence and splice acceptor site for the tat-III

gene of HTLV-III.

B. Cohen's claims corresponding to Count 1

We proceed to reconsider the patentability of Claims 1-43 of Cohen's U.S. 5,276,019 under 35 U.S.C. § 103 (1) in view of the combined teachings of prior art including Goodchild's U.S. 4,806,463, which issued February 21, 1989, from Application 06/867,231, filed May 23, 1986 (Goodchild Exh. 1002), Eckstein I (Goodchild Exh. 1003) and Eckstein (II)(Goodchild Exh. 1004), optionally further in view of Stec (Goodchild Exh. 1009); and (2) in view of the teachings of Zamecnik's NIH Grant Application (Cohen Exh. 2039), optionally further in view of Stec (Goodchild Exh. 1009). We have concluded supra that Goodchild's '463 patent is prior art to Claims 1-43 of Cohen's '019 patent under 35 U.S.C. § 102(e) and Zamecnik's NIH Grant Application is prior art under 35 U.S.C. § 102(a). However, we have also concluded that neither reference is prior art to Claims 1-43 of Cohen's '019 patent under 35 U.S.C. § 102(b). We must consider all the evidence of record for, and all the evidence against, the patentability of Claims 1-43 of Cohen's '019 patent and Claims 1-48 of Cohen's '423 patent.

On request for reconsideration (Paper No. 110), Cohen argues that the Board overlooked key pieces of non-obviousness evidence and misapprehended the cumulative import of all the

non-obviousness evidence (Paper No. 110, pp. 19-20). More particularly, Cohen argues that the Board did not grant sufficient weight to the evidence teaching away from the invention of Cohen's claims corresponding to Count 1 (Paper No. 110, pp. 20-24). Cohen's arguments are supported by declarations of persons highly skilled in the art (Cohen Exhs. 2048 and 2049), buttressed by statements by opposing Drs. Zamecnik and Goodchild (Cohen Exh. 2063, pp. 2-3), explaining why the prior art would have, and appears to have, led persons skilled in the art away from the subject matter Cohen claims. Cohen alleges that success achieved using the invention Cohen claims reasonably would not have been expected at the time the invention was made and points to the evidence of commercial success further in support of that allegation. The Board appears to have considered the same evidence, but it did so primarily as it relates to the scope and content of the subject matter claimed in Cohen's U.S. 5,264,423 (Goodchild Exh. 1001). While the Board stated that the scope and content of the subject matter claimed in Cohen's U.S. 5,276,019 (Goodchild Exh. 1014) was narrower in scope than the subject matter claimed in Cohen's U.S. 5,264,423 (Goodchild Exh. 1001), it granted Goodchild's Preliminary Motion 2 "for the reasons set forth with respect to Goodchild's Preliminary Motion 1" (Paper No. 104, pp. 56-58), without

considering the particular subject matter of the narrower claims.

When considering the patentability of the subject matter claimed in Cohen's patents, it is important to remember that a showing which is not commensurate in scope with the broader claims of Cohen's patents may yet be commensurate in scope with the narrow claims. Another important consideration is that the patentability of much of the subject matter claimed in Cohen's '019 patent is to be determined as of the March 25, 1987, filing date of Application 07/030,073 rather than the February 22, 1988, the earliest filing date to which the subject matter claimed in Cohen's '423 patent has been accorded benefit under 35 U.S.C. § 120. Cohen has not challenged the § 120 benefit the Board accorded its '423 patent. Thus, the underlying findings and conclusions of the Board's decision as to the patentability of the broader claims of Cohen's '423 patent, and the adequacy of the evidence submitted in support of the patentability of those claims, should not have been summarily relied upon by the Board when considering the patentability of the narrower claims of Cohen's '019 patent.

While the burden of proof may have shifted to Cohen to rebut any prima facie case of unpatentability established by Goodchild for its broader claims, Goodchild had the initial burden to show that it was entitled to the relief sought in Goodchild's

Preliminary Motions 1-6. Accordingly, we proceed to reconsider Goodchild's case for unpatentability of Claims 1-43 of Cohen's '019 patent aside from Goodchild's case for unpatentability of the broader scope of subject matter defined by Claims 1-48 of Cohen's '423 patent under 35 U.S.C. § 103 in view of any combination of the teachings of Goodchild's U.S. 4,806,463 (Goodchild Exh. 1002), Zamecnik's NIH Grant Application (Cohen Exh. 2039), Eckstein (I)(Goodchild Exh. 1003), Eckstein (II) (Goodchild Exh. 1004) and Stec (Goodchild Exh. 1009).

While Goodchild teaches that useful antisense oligonucleotides may be modified at a variety of locations along their length, including modification on the internal phosphate groups (Goodchild Exh. 1002, col. 5, l. 29-33), the reference teaches further that the kind and location of the modification depends on many factors (Goodchild Exh. 1002, col. 5, l. 33-40):

> Whether oligonucleotides to be used are modified and, if so, the location of the modification(s) will be determined, for example, by the desired effect on the viral activity (e.g., inhibition of viral replication, gene expression or both), uptake into the infected cells, inhibition of degradation of the oligonucleotides once they are inside cells, and prevention of their use as a primer by reverse transcriptase.

Goodchild's concern with oligonucleotide degradation focussed on "degradation of the oligonucleotides <u>once they are inside cells</u>" (Goodchild Exh. 1002, col. 5, l. 39; emphasis added). Similarly,

we find that persons having ordinary skill in the art would have been concerned with oligonucleotide degradation inside of virus-infected cells due to the oligonucleotide's capacity to inhibit virus replication and/or gene expression inside the infected cells.

Goodchild stated that cell uptake of antisense oligonucleotides may be increased by addition of lipophilic groups to the antisense oligonucleotide (Goodchild Exh. 1002, col. 5, l. 48-52). We find that persons skilled in the art would have expected lipophilic groups added to oligonucleotides to impart nonionic characteristics to the oligonucleotides.

Zamecnik's NIH Grant Application (Cohen Exh. 2039) further leads away from the subject matter claimed in Cohen's '019 application. In its Introduction 1a, Zamecnik states (U.S. Exh. 2039, Introduction 1a, second full para.; emphasis added):

> The employment of synthetic oligodeoxyribonucleotides complementary to conserved critical segments of the primary nucleotide structure of viruses as a potential chemotherapeutic mechanisms [sic] was pioneered by the Worcester Foundation group, using Rous sarcoma virus. This approach has had initial success in inhibiting HTLV-III replication and expression in experiments already under way in collaboration with the Gallo-Sarin laboratory at the NIH. One of the key limitations however, is that oligodeoxynucleotides of the order of 20 monomer units penetrate the cell membrane at low levels - around a few percent of the exterior concentration, within the time span of minutes to a few hours. <u>It is clear from published work of Miller and Ts'o that abolition of the internucleotide phosphate negative charge by modification</u>

> as the phosphonate analogue improves cell permeability by a factor approaching ten fold. . . . . Dr. Letsinger has also been particularly interested in devising new modifications of oligomers to improve their cell penetrability. . . . .

The import of cell penetrability is evident from Zamecnik's statement that newly synthesized "modified oligomers . . . will be screened for relative facility of cell penetrability" (Cohen Exh.2039, Introduction 2, para. 2). Moreover, Zamecnik's Abstract of Research Plan states (Cohen Exh.2039, p. 2; emphasis added):

> Our current studies strongly suggest that intact 12-20 mer oligodeoxynucleotides penetrate eukaryotic cells in culture at a level of a few percent of the external concentration. We will study the effect of length of oligomer and abolition of the negative charge of the internucleoside phosphates on cell permeability by oligomers. A variety of new modifications of internucleoside phosphates and lipophilic adducts are being made by Professor Letsinger's laboratory. Testing of their influence on cell permeability and resistance to intracellular nucleases will be done in our laboratory.

Zamecnik aims specifically (Cohen Exh.2039, p. 21, para. 2; emphasis added):

> To compare the inhibitory effect of complementary unmodified oligomers . . . with oligomers with various modifications, including internucleotide phosphate analogues and lipophilic groups. The latter (synthesized by Professor Letsinger's group) are designed to improve cell permeability by increased lipophilicity or by abolition of the negative charge of the phosphate group, to resist nuclease degradation of the oligomers, both intracellularly and extracellularly, and yet to maintain an effective complementary hybridization potential.

According to Zamecnik's NIH Application Grant, a most significant question is whether the antisense oligodeoxynucleotide will enter a lymphocyte in sufficient amounts to hybridize effectively with the viral genome, and withstand degradation long enough to provide an inhibitory effect (Cohen Exh.2039, p. 21, para. 4).

Zamecnik's NIH Application Grant stresses (Cohen Exh. 2039, p. 24, second full para.):

> Unlike the use of endogenously transcribed or microinjected anti-sense RNA's, inhibition of viral replication by
>
> exogenous oligodeoxynucleotides appears to depend upon uptake of sufficient amounts by the cells.

Focussing on possible "Internucleotide phosphate and other modifications," Zamecnik stated, "This may be the most desirable function to block as the resulting, non-charged oligonucleotides are taken up by cells more readily, are more resistant to enzymatic degradation, and retain the ability to form Watson-Crick base pairs . . ." (Cohen Exh. 2039, p. 28; emphasis added). More particularly, Zamecnik expressed the following intentions, direction, and concerns ((Cohen Exh. 2039, p. 28):

> In our laboratory, we intend to use the procedure of Miller et al. to synthesize oligonucleotide methyl phosphonates (22) [Murakami et al., Biochemistry, Vol. 24, pp. 4041-4046 (1985) (Cohen Exh. 2039, p. 34]. A third phosphate modification, the replacement of P=O by P=S, does not alter the charge on the molecule but may increase

> resistance to degradation (23)[12]. This modification can be introduced during automatic synthesis (24) [Stec et al., Tetrahedron Letters, Vol. 25, pp. 5279-5282 (1984)].
>
> As phosphate modification can result in solubility problems, it will be necessary to investigate the ratio of modified to unmodified phosphates to optimize activity.

As we previously found, Miller, U.S. 4,511,713 (Goodchild Exh. 1028), is directed to nonionic, complementary oligonucleotide analogues designed to (1) easily pass though the membranes of living cells, (2) resist degradation by nuclease enzymes found within cells, and (3) strongly interact with complementary polynucleotides found inside the cell to form stable complexes therewith (Goodchild Exh. 1028, cols. 1-2). Smith's May 1986 article approached antiviral chemotherapy by developing "sequence-specific nonionic nucleic acid analogues that contain a 3'-5' methylphosphonate group in place of the negatively charged phosphodiester group normally found in oligonucleotides . . . [because t]hese analogues [sic] are resistant to nuclease hydrolysis and penetrate mammalian cells in culture . . . (Cohen Exh. 2135, p. 2787, col. 1 second para.).

The evidence of record, considered as a whole, strongly suggests that persons having ordinary skill in the art at the time Cohen made the invention claimed in Cohen's '019 patent

---

[12] There is no corresponding citation at Cohen Exh. 2039, p. 34; Reference 23 in the citations at the end of Zamecnik's NIH Grant Application is blank.

reasonably would not have expected that phosphorothioate-modified antisense nucleotide sequences complementary to RNA or DNA of a virus would inhibit replication or cytopathic effect in a host for the following reasons. First, persons having ordinary skill in the art would have recognized that phosphorothioate-modified antisense nucleotide sequences are ionic. Second, although the prior art clearly taught that phosphorothioate-modified antisense nucleotide sequences are resistant to degradation by nuclease enzymes, persons having ordinary skill in the art reasonably would not have expected that ionic, phosphorothioate-modified antisense nucleotide sequences could penetrate virus-infected cells in amounts sufficient to inhibit the replication or cytoplasmic effect of a virus in virus-infected cells. Third, persons having ordinary skill in the art reasonably would not have expected phosphorothioate-modified antisense nucleotide sequences to successfully inhibit the replication or cytoplasmic effects of a virus in virus-infected cells without the capacity to penetrate virus-infected cells in quantities sufficient to inhibit the replication or cytoplasmic effect of the virus therein.

We are mindful of the Board's preliminary opinion that, in order to establish the obviousness of the subject matter Cohen claims, it is sufficient that the prior art would have led

persons having ordinary skill in the art to reasonably expect that phosphorothioate-modified antisense nucleotide sequences have the capacity to inhibit the replication or cytoplasmic effect of a virus. Nevertheless, neither Goodchild, the Board, nor persons having ordinary skill in the art may disregard significant claim language, functional or otherwise, which requires that the claimed phosphorothioate-modified antisense nucleotide sequences inhibit the replication or cytopathic effect of a complementary nucleotide sequence "in a host" (see Claims 1-43 of Cohen's '019 patent (Goodchild Exh. 1014) and Claims 1-48 of Cohen's '423 patent (Goodchild Exh. 1001)). In short, while persons having ordinary skill in the art might have been motivated by the prior art teaching to make phosphorothioate modified antisense nucleotide sequences and attempt to use them to inhibit the replication or cytoplasmic effect of a virus in virus-infected host cell, they reasonably would not have expected the phosphorothioate modified antisense nucleotide sequences to successfully inhibit the replication or cytoplasmic effect of a virus in a virus-infected cell without evidence that they can penetrate a virus-infected host cell in amounts sufficient to inhibit the replication or cytoplasmic effect of the virus in the virus-infected cell.

We hold that the Board undervalued the significance of the

phrases "inhibit . . . in a host" both in Claims 1-43 of Cohen's '019 patent and Claims 1-48 of Cohen's '423 patent in determining that Cohen's claims would have been obvious to persons having ordinary skill in the art in view of the applied prior art, at least to the extent the Board granted Goodchild's Preliminary Motions 1, 2, 4, and 5. Accordingly, we defer our disposition of Goodchild's Preliminary Motions 1, 2, 4, and 5 to final hearing to give the parties a full and fair opportunity to respond to the analysis we have set out in this decision on reconsideration.

9. Patentability of the parties' claims under 35 U.S.C. § 112

Our decisions on Cohen's Preliminary Motion 7 (Paper No. 115) and reconsideration of the Board's decisions denying Cohen's Preliminary Motions 3 (Paper No. 46) and 4 (Paper No. 47) are deferred to final hearing. We will consider the matters as required at final hearing. The matters are best considered in light of all the arguments and evidence the parties bring in response to the new positions taken herein with regard to the patentability of the parties' claims corresponding to the count under 35 U.S.C. § 103, the benefits accorded the parties' claims under 35 U.S.C. §§ 119 and 120, and the sufficiency under 35 U.S.C. § 112, first paragraph, of the parties' disclosures in support of their respective claims corresponding to the count.

10. Substituting new Count 2 for existing Count 1

Given our deliberations hereinabove, and the findings and conclusions resulting therefrom, we now see Count 1 of this interference in a new light. It is apparent from the evidence of record that Count 1, aside from newly raised patentability issues, is directed to at least two patentably distinct inventions. The first of these is an ionic oligonucleotide capable of inhibiting the replication or cytopathic effect of a virus in a host consisting of a nucleotide sequence complementary to a region of RNA or DNA of the virus necessary for its replication or gene expression, wherein at least one of the internal phosphate groups is modified such that P=O is replaced by P=S. The second of these is a nonionic oligonucleotide capable of inhibiting the replication or cytopathic effect of a virus in a host consisting of a nucleotide sequence complementary to a region of RNA or DNA of the virus necessary for its replication or gene expression, wherein at least one of the internal phosphate groups is modified such that the modified internal phosphate groups do not prevent the complementary nucleotide sequence from inhibiting the replication or cytopathic effect of a virus in a host.

Both parties to this interference present claims directed to the first invention, which is represented by

ionic phosphorothioate antisense oligonucleotide analogues complementary to selective nucleotide sequences of HTLV-III.

Only Goodchild presents claims directed to the second invention, which is represented by nonionic methylphosphonate antisense oligonucleotide analogues complementary to selective nucleotide sequences of HTLV-III.

The first invention appears to be patentably distinct from the second. The second invention appears to be unpatentable to Goodchild over prior art - but Cohen does not claim to be an inventor of subject matter that interferes with the second invention. On the other hand, claims directed to the first invention reasonably appear to be patentable to Cohen over prior art, Goodchild claims to be an inventor thereof, and aside from Cohen's prior art disclosure, Goodchild's claims appear to be patentable to Goodchild.

Accordingly, the purpose of this interference proceeding is most properly and effectively served by restricting the interference proceeding to said first invention, the only invention likely to be patentable to either party.

Conclusions

We have reconsidered the Board's Decisions On Preliminary Motions and Order (Paper No. 104) based on all the evidence of record. To the extent the findings and conclusions of our

earlier decision are different from, inconsistent with, or new to this decision on reconsideration, they are superseded by the findings and conclusions entered herein. To the extent we are silent, we adopt the earlier findings and conclusions. Accordingly, for reasons stated herein, or adopted hereby, it is

ORDERED that:

A. Goodchild's Preliminary Motion 1 (Paper No. 33) is deferred to final hearing.

B. Goodchild's Preliminary Motion 2 (Paper No. 34) is deferred to final hearing.

C. Goodchild's Preliminary Motion 3 (Paper No. 35) is denied.

D. Goodchild's Preliminary Motion 4 (Paper No. 36) is deferred to final hearing.

E. Goodchild's Preliminary Motion 5 (Paper No. 37) is deferred to final hearing.

F. Goodchild's Preliminary Motion 6 (Paper No. 38) is denied.

G. Goodchild's Preliminary Motion 8 (Paper No. 40) is deferred to final hearing.

H. Goodchild's Preliminary Motion 9 (Paper No. 41) is denied. For reasons stated herein with regard to the patentability of Goodchild's pending claims designated as

corresponding to Count 1, Goodchild has not established that the subject matter defined by the proposed Claims 71 to 82 is patentable to Goodchild.

I. Goodchild's Preliminary Motion 10 (Paper No. 53) is dismissed.

J. Cohen's Preliminary Motion 1 (Paper No. 44) is dismissed. We substitute a new, narrower Count 2 hereinafter which renders Cohen's motion to substitute a narrower count and the reasons therefor moot.

K. Cohen's Preliminary Motion 2 (Paper No. 45) is dismissed.

L. Cohen's Preliminary Motion 3 (Paper No. 46) is deferred to final hearing.

M. Cohen's Preliminary Motion 4 (Paper No. 47) is deferred to final hearing.

N. Cohen's Preliminary Motion 5 (Paper No. 48) is denied.

O. The Sua Sponte Actions Pursuant To 37 CFR § 1.641(a) and Order Pursuant to 37 CFR § 1.641(a) and reasons therefor entered at pages 100 to 106 of the Board's Decisions On Preliminary Motions and Order (Paper No. 104) are withdrawn.

P. Final decisions as to the patentability under 35 U.S.C. § 103 of Goodchild's claims designated as corresponding to

Count 1 in view of prior art raised for the first time herein are deferred to final hearing. The parties are authorized to submit arguments and evidence in support of their arguments relating to the new grounds of rejection in, and in support of, their respective briefs at final hearing.

Q. Cohen's Preliminary Motion 7 (Paper No. 115) is deferred to final hearing.

R. Interference 105,040 is redeclared as set forth the the separate order mailed with this decision.

FURTHER ORDERED that all times remain in effect.

FURTHER ORDERED that if there is a settlement, the attentions of the parties are directed to 35 U.S.C. § 135(c) and 37 CFR § 41.205.

TEDDY S. GRON)
Administrative Patent Judge)
)
)
)
SALLY GARDNER LANE) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
)
)
MARK NAGUMO)
Administrative Patent Judge)

Date: 13 Dec 2004
Alexandria, VA

Interference 105,040
Cohen v. Goodchild

Attorney for Cohen
(Real party in interest
assignee United States of America, as represented by the Department of Health and Human Services, Office of Technology Transfer)

Guy Chambers, Esq.
Steven W. Parmelee, Esq.
TOWNSEND and TOWNSEND and CREW, LLP
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834
Tel. 415-576-0200
Fax: 415-576-0300

Attorney for Goodchild
(Real party in interest
assignee University of Massachusetts, Worcester)

Michael Sofocleous, Esq.
3975 University Drive, Suite 330
Fairfax, VA 22030
Tel. 703-246-9645 (703) 623-1395 (Cell)
Fax 703-246-9646